To: Jordan, William[Jordan.William@epa.gov]
Cc: Housenger, Jack[Housenger.Jack@epa.gov]; Vogel, Dana[Vogel.Dana@epa.gov]
From: Rowland, Jess
Sent: Mon 4/6/2015 4:27:38 PM
Subject: RE: Three follow up glyphosate questions
CPRC II.pdf

Hi Bill

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Excerpt from the SAP Report

Panel Response:

In the instance of Glyphosate, the Panel on renal tumors in male mice are equivocal. tumors were found in any group, including tho which appear to have exceeded the maximal tol majority of the pathologists, who examined th in the male control animal, agreed that the l renal adenoma. Therefore, statistical analys utilize this datum. In addition, the statist age-adjusted; when this is done, no oncogenic is demonstrated using concurrent controls. N currence of three neoplasms in high dose male using historical controls is statistically hi thermore, categorization of the oncogenic ris plicated by the fact that doses used in the r to have reached the maximal tolerated dose. the Panel does not believe that it is possibl sate clearly into Group C (possible human car evidence of carcinogenicity for humans). The Glyphosate be categorized as Group D (not cla be a data call-in for further studies in rats unresolved questions.

Regarding the issue of using historical the Panel believes that this has to be decide For Glyphosate, the historical control data reason for concern. However, the level of co cal control data was not great enough to dis emphasis on the concurrent controls.

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Jordan, William
Sent: Friday, April 03, 2015 4:50 PM
To: Rowland, Jess; Miller, David
Subject: RE: Three follow up glyphosate questions

Thanks. If you can look into it on Monday morning, that is soon enough.

Enjoy the day at the museum.

And the lovely weekend too.

Bill

William Jordan

Deputy Director, Programs

Office of Pesticide Programs

U. S. Environmental Protection Agency

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Courier Address:
Potomac Yards South
2777 Crystal Drive
Room 12-235
Arlington, VA

From: Rowland, Jess
Sent: Friday, April 03, 2015 4:40 PM
To: Jordan, William; Miller, David
Subject: RE: Three follow up glyphosate questions

Ex. 5 - Deliberative Process

Sent from my Windows Phone

From: Jordan, William
Sent: 4/3/2015 3:26 PM
To: Rowland, Jess; Miller, David
Subject: FW: Three follow up glyphosate questions

Another question from the NYT folks. Again I would appreciate your help.

Thanks,

Bill

William Jordan

Deputy Director, Programs

Office of Pesticide Programs

U. S. Environmental Protection Agency

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2777 Crystal Drive
Room 12-235
Arlington, VA

From: Boffey, Philip [mailto:phboff@nytimes.com]
Sent: Friday, April 03, 2015 3:24 PM
To: Jordan, William
Cc: Milbourn, Cathy; Daguillard, Robert
Subject: Re: Three follow up glyphosate questions

Sooner is always better.

Did you deal with that odd matter where the IARC seems to have decided that EPA's 1991 report did show significant increases in cancer in laboratory animals contrary to the agency's analysis at the time. They refer to an EPA Scientific Advisory Report which apparently said the results were significant using two statistical tests that IARC recommends.

On Fri, Apr 3, 2015 at 3:12 PM, Jordan, William <Jordan.William@epa.gov> wrote:

Thanks. **Ex. 6 - Personal Privacy**

I have put our answers into the clearance process. They should definitely be to you by Monday, but Robert or Cathy may be able to send them sooner.

Have a good weekend.

Bill

William Jordan

Deputy Director, Programs

Office of Pesticide Programs

U. S. Environmental Protection Agency

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Room 12-235
Arlington, VA

From: Boffey, Philip [mailto:phboff@nytimes.com]
Sent: Friday, April 03, 2015 3:05 PM

To: Jordan, William
Cc: Milbourn, Cathy; Daguillard, Robert
Subject: Re: Three follow up glyphosate questions

Hi Bill,

My editorial on glyphosate has been postponed until next week so I don't need your answers until Monday. No harm in sending something earlier but the pressure is off if you're feeling lousy or have hit a stumbling block.

Phil

On Fri, Apr 3, 2015 at 7:36 AM, Philip Boffey <phboff@nytimes.com> wrote:

Great. Thanks. Ex. 6 - Personal Privacy

Sent from my iPhone

On Apr 3, 2015, at 7:30 AM, "Jordan, William" <Jordan.William@epa.gov> wrote:

Ex. 6 - Personal Privacy but I will try to send answers before noon.

Thanks

Bill

Sent from my Windows Phone

From: Philip Boffey
Sent: 4/2/2015 9:33 PM
To: Jordan, William
Cc: Milbourn, Cathy
Subject: Three follow up glyphosate questions

Hi Bill,

In looking more closely at the Lancet Oncology summary and a two-page IARC summary issued the same day (March 20), I see they say there is convincing evidence that glyphosate can cause cancer in laboratory animals as well as DNA or chromosomal damage in human and animal cells. One study of residents in several communities where glyphosate was sprayed found increases in blood markers for chromosomal damages.

1) Was EPA aware of these studies? Did you also conclude

there was nothing in them that would change your 1991 conclusions, as you did with the 55 epidemiological studies?

2) Would I be out on a limb to declare on my own authority (not attributed to the agency) that it seems unlikely EPA will change its 1991 judgment that glyphosate is probably not a human carcinogen?

3) An editor asks whether overuse of glyphosate has led to widespread emergence of glyphosate-resistant weeds. Is that an issue that EPA considers in regulating pesticides?

An answer tomorrow morning would be greatly appreciated.

Phil Boffey

Sent from my iPad

--

Philip M. Boffey

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

008898

OCT 30 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: SECOND Peer Review of Glyphosate

CAS No. 1071-83-6
EPA Chem. Code 417300
40 CFR 180.364
TOX Chem. No.: 661A
Reg Group: List A (6B)

FROM: William Dykstra, Ph.D. William Dykstra
Toxicology Branch I (IRS)
Health Effects Division (H7509C)

and

George Z. Ghali, Ph.D. G. Ghali 8/22/91
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Lois Rossi, Chief
Reregistration Branch
Special Review and Reregistration Division (H7508W)

The Health Effects Division Carcinogenicity Peer Review Committee convened on June 26, 1991 to discuss and evaluate the weight of the evidence on Glyphosate with particular emphasis on its carcinogenic potential. The Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based upon lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

1

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A. Individual in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated.)

Penny Fenner-Crisp	Penelope J. Fenner-Crisp
William L. Burnam	
Karl Baetcke	
Marcia Van Gemert	Marcia van Gemert
Esther Rinde	
Hugh Pettigrew	
Marion Copley	Marion P. Copley
Lucas Brennecke	
George Ghali	

2. Peer Review Members in Absentia (Committee members who were unable to attend the discussion; signature indicates concurrence with the overall conclusions of the Committee.)

Reto Engler	
Richard Hill	—
John Quest	
Kerry Dearfield	
Yin-Tak Woo	
Jean Parker	— NONCONCUR
William Sette	
Robert Beliles	DO NOT CONCUR
Julie Du	

3. Scientific Reviewers (Committee or noncommittee members responsible for data presentation; signature indicates technical accuracy of panel report.)

William Dykstra	
Roger Gardner	9-5-91

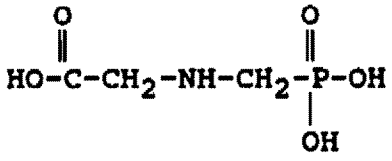
B. Background Information

Glyphosate is the isopropylamine (IPA) or sodium salt of N-(phosphonomethyl) glycine, marketed under the trade names of Roundup, Rodeo, Shackle, and Polado. Glyphosate is a wide spectrum plant growth regulator herbicide which is used to control grasses, sedges, and broadleaf weeds. It acts by the inhibition of amino acid synthesis.

Tolerances established for glyphosate and its aminomethyl phosphonic acid (AMPA) metabolite in 40 CFR 180.364 include the following:

IPA salt of glyphosate: soybeans, cotton, corn, sorghum, wheat, rice, vegetables, citrus fruits, pome fruits, stone fruits, tropical fruits, pastures, and alfalfa.

Sodium salt of glyphosate: sugarcane.



Glyphosate

On February 11, 1985, the carcinogenic potential of glyphosate was first considered by a panel (then called the Toxicology Branch Ad Hoc Committee) comprised of members of the Toxicology Branch of the Hazard Evaluation Division. The Committee, in a consensus review dated March 4, 1985, classified glyphosate as a Group C carcinogen based on an increased incidence of renal tubular adenomas in male mice. According to the consensus review, the tumor is rare, it occurred in a dose-related manner, and the incidence was outside the reported historical control range. The Committee also concluded that dose levels tested in a 26-month rat feeding study were not adequate for the assessment of glyphosate's carcinogenic potential in this species.

The kidney slides from the long-term mouse feeding study were subsequently reexamined, and one pathologist diagnosed an additional kidney tumor in control males. These findings were presented to the FIFRA Scientific Advisory Panel (SAP) which proposed that glyphosate be classified into Group D (inadequate animal evidence of carcinogenic potential). The SAP, in their meeting of February 11-12, 1986 (report dated February 24, 1986), concluded that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of

these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

HED deferred a decision on the repeat of an additional mouse oncogenicity study until the 1990 rat feeding study had been evaluated by the Peer Review Committee.

C. Material Evaluated

The material available for review consisted of a document prepared by Dr. William Dykstra summarizing major scientific and regulatory issues and relevant toxicology information, data evaluation records of a combined chronic toxicity/carcinogenicity study in rats and a carcinogenicity study in mice, the FIFRA Scientific Advisory Panel report dated Feb 24, 1986, a review of historical control data on mouse kidney tumors, a toxicology one-liner for the glyphosate data base and an OPP peer review report entitled "Consensus Review of Glyphosate" dated March 4, 1985.

D. Evaluation of Carcinogenicity Data

1. **Lankas, G. P. December 23, 1981. A Lifetime Study of Glyphosate in Rats. Unpublished report No. 77-2062 prepared by BioDynamics, Inc. EPA Acc. Nos. 247617 - 247621. MRID 00093879.**

a. Experimental Design

The lifetime feeding study in Sprague-Dawley rats at 50/sex/dose was conducted at dietary concentrations of glyphosate of 0, 30, 100, and 300 ppm. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in female rats were maintained.

b. Discussion of Tumor Data

An increase in the incidence of interstitial cell tumors of the testes was observed in male rats. Because of the absence of a dose-response relationship, the lack of preneoplastic changes, the wide variability in the spontaneous incidence of this tumor, the similarity in incidences between the high-dose

group and the historical controls, and lack of any evidence of genotoxicity, it was concluded by the previous Peer Review Committee that the observed incidence did not reflect a carcinogenic response.

Additionally, there was the question of possible thyroid carcinomas in high-dose females. After a review of the slides by a consulting pathologist, and a reassessment of all relevant data, including the fact that no effect of treatment on tumor latency or the combined incidences of adenoma and carcinoma was apparent, the earlier Peer Review Committee concluded that the data did not demonstrate a carcinogenic response in the thyroid.

c. Nonneoplastic Lesions and Adequacy of Dosing Considerations

No effect of treatment on the incidence of nonneoplastic lesions was noted. No effects of treatment on survival, body weight gain, clinical pathology, or findings at necropsy were noted. Therefore, there is no evidence that the highest dose tested was adequate to evaluate the carcinogenic potential of glyphosate.

2. **Stout, L. D. and Ruecker, F. A. (1990). Chronic Study of glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; Sept. 26, 1990. MRID No. 416438-01; Historical Controls; MRID No. 417287-00.**

a. Experimental Design

This chronic toxicity/carcinogenicity study in the rat was submitted to the Agency as a replacement study for the 26-month 1981 chronic toxicity/carcinogenicity study in the rat. In this study, randomized groups of 60 male and 60 female young (8 weeks old) Sprague-Dawley rats were fed dietary levels of 0, 2000, 8000, or 20,000 ppm or the equivalent of 0, 100, 400, and 1000 mg/kg/day of technical glyphosate for 2 years. At 12 months, 10 animals/sex/group were sacrificed.

b. Discussion of Tumor Data

Age-adjusted, statistical analyses of the tumor data are presented. The most frequently observed tumors in this study were pancreatic islet cell adenomas in males, thyroid C-cell adenomas and/or carcinomas in males and females, and hepatocellular adenomas and carcinomas in males. The following is a discussion of each type of tumor.

i. Pancreas (Tables 1 - 3)

Low-dose and high-dose males had a statistically significant increased incidence of pancreatic islet cell adenomas.

Table 1: Glyphosate - Sprague-Dawley Male Rats, Pancreatic Islet Cell Tumor Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	1/43[a]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
p =	0.159	0.409(n)	0.467(n)	0.472(n)
Adenomas	1/43	8/45	5/49	7/48[b]
(%)	(2)	(18)*	(10)	(15)*
p =	0.170	0.018*	0.135	0.042*
Adenomas/carcinomas	2/43	8/45	5/49	7/48
(%)	(5)	(18)	(10)	(15)
p =	0.241	0.052	0.275	0.108
Hyperplasia only	2/43	0/45	3/49	2/48[c]
(%)	(5)	(0)	(6)	(4)
p =	0.323	0.236	0.526	0.649

* Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

[a] First carcinoma observed at week 105, dose 0 ppm.

[b] First adenoma observed at week 81, dose 20000 ppm.

[c] First hyperplasia observed at week 91, dose 20000 ppm.

[d] $p \leq 0.05$; Fisher's Exact test with Bonferoni correction.

Note:
Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Historical control data on the incidence of pancreatic islet cell adenomas from Monsanto's EHL are shown in Table 2 below.

Table 2: EHL 87122 - Historical Control Information for Histopathological Findings (All Deaths)

Terminal Necropsy Study	Months of Date	Study Length (Months)	No. Observed	No. Affected	% Affected
1	07/83	24	68	2	2.9
2	02/85	23	59	5	8.5
3	10/85	24	69	4	5.8
4	06/85	24	57	1	1.8
5	09/88	24	60	5	8.3
6	01/89	24	60	3	5.0
7	03/89	24	59	3	5.1

Committee's interpretation: Although the incidences of the pancreatic islet cell adenomas at the low-, mid- and high-dose groups exceeded the historical control range of 1.8 to 8.5 percent in male rats, there was no statistically significant positive dose-related trend in the occurrence of these tumors in males, no progression to carcinoma, and the incidence of hyperplasia was not dose-related. Therefore, the pancreatic islet cell tumors were not considered to be compound-related. It was also noted that the incidence of this lesion in the concurrent control for males was at the low end of the historical control range. The Committee concluded that the apparent statistical significance of the pairwise comparisons of the treated male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response.

The incidences of islet cell pancreatic tumors in the earlier rat study (Bio/dynamics Project No. 77-2062) are shown in Table 3. The incidence of pancreatic islet cell tumors for the two studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

Table 3: Incidence of Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Given Diets Containing Glyphosate for 26 Months (first rat feeding study).

Tumors	Dose (mg/kg/day) 0	3	10	30
Hyperplasia (%)	3/50 (6)	2/49 (4)	1/50 (2)	0/50 (0)
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Adenoma/carcinoma (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

ii. Thyroid (Tables 4 - 6)

C-cell adenomas were slightly increased in male and female mid- and high-dose groups as shown in Tables 4 and 5. Historical control ranges for the thyroid tumors in Sprague-Dawley rats were reported as shown in Table 6.

Committee's interpretation: Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

Table 4: Glyphosate - Sprague-Dawley Male Rats, Thyroid C-Cell Tumor Rates* and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	0/54	2/55[a]	0/58	1/58
(%)	(0)	(4)	(0)	(2)
p =	0.452	0.252	1.000	0.518
Adenomas	2/54[b]	4/55	8/58	7/58
(%)	(4)	(7)	(14)	(12)
p =	0.069	0.348	0.060	0.099
Adenoma/carcinoma	2/54	6/55	8/58	8/58
(%)	(4)	(11)	(14)	(14)
p =	0.077	0.141	0.060	0.060
Hyperplasia only	4/54	1/55	5/58[c]	4/58
(%)	(7)	(2)	(9)	(7)
p =	0.312	0.176	0.546	0.601

---

[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 54 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

* Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Table 5: Glyphosate - Sprague-Dawley Female Rats, Thyroid C-Cell Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Tests Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	0/57	0/60	1/59[a]	0/55
(%)	(0)	(0)	(2)	(0)
p =	0.445	1.000	0.509	1.000
Adenomas	2/57	2/60	6/59[b]	6/55
(%)	(4)	(3)	(10)	(11)
p =	0.031*	0.671(n)	0.147	0.124
Adenoma/carcinoma	2/57	2/60	7/59	6/55
(%)	(4)	(3)	(12)	(11)
p =	0.033*	0.671(n)	0.090	0.124
Hyperplasia only	10/57[c]	5/60	7/59	4/55
(%)	(18)	(8)	(12)	(7)
p =	0.113	0.112	0.274	0.086(n)

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[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 72 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

[+] Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

(n) Negative change from control.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Table 6: Historical Control Data for the Incidence of Thyroid C-Cell Tumors in Sprague-Dawley Strain Rats.

Tumor	Range (%) Males	Females
Carcinomas	0.0 - 5.2	0.0 - 2.9
Adenomas	1.8 - 10.6	3.3 - 10.0
Hyperplasia	4.3 - 20.0	4.3 - 16.9

iii. Liver (Table 7)

There was a slight dose-related increase in hepatocellular adenomas in males but the incidence was within the range of historical controls from Monsanto's EHL. The reported historical control incidence of hepatocellular carcinomas ranged from 0 to 6.7%, and that for hepatocellular adenomas ranged from 1.4 to 18.3%. There were no dose-related increases in the incidences of other hepatocellular lesions.

Table 7: Glyphosate - Sprague-Dawley Male Rats, Hepatocellular Tumor Rates* and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

Tumors	Dose (ppm) 0	2000	8000	20,000
Carcinomas	3/44	2/45	1/49	2/48[a]
(%)	(7)	(4)	(2)	(4)
p =	0.324	0.489(n)	0.269(n)	0.458(n)
Adenomas	2/44	2/45	3/49	7/48[b]
(%)	(5)	(4)	(6)	(15)
p =	0.016	0.683(n)	0.551	0.101
Adenoma/carcinoma	5/44	4/45	4/49	9/48
(%)	(11)	(9)	(8)	(19)
p =	0.073	0.486(n)	0.431(n)	0.245
Hyperplasia only	0/44	0/45	1/49[c]	0/48
(%)	(0)	(0)	(2)	(0)
p =	0.462	1.000	0.527	1.000

[a] First carcinoma observed at week 85 at 20,000 ppm.

[b] First adenoma observed at week 88 at 20,000 ppm.

[c] First hyperplasia observed at week 89 at 8000 ppm.

* Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Committee's interpretation: Despite the slight dose-related increase in hepatocellular adenomas in males, this increase was not significant in the pair-wise comparison with controls and was within the historical control range. Furthermore, there was no progression from adenoma to carcinoma and incidences of hyperplasia were not compound-related. Therefore, the slightly increased occurrence of hepatocellular adenomas in males is not considered compound-related.

c. Nonneoplastic lesions

There were no compound-related nonneoplastic lesions.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The HDT was 20,000 ppm which is the limit dose for carcinogenicity testing in rats. However, it appears that animals could have tolerated higher doses.

3. **Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamics Inc., dated July 21, 1983. Report No. 77-2061. EPA Acc. Nos. 251007 - 251009, and 251014.**

a. Experimental Design

Groups of 50 male and 50 female CD-1 mice were administered glyphosate in the diet at concentrations of 1000, 5000, or 30,000 ppm for 18 months.

b. Discussion of Tumor Data

Glyphosate produced an equivocal carcinogenic response in males characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

The Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee, in their meeting of February 11, 1985, tentatively classified glyphosate as a "Class C" carcinogen (report dated March 4, 1985). The kidney slides were reexamined by a consulting pathologist, and data were submitted indicating that an additional kidney tumor had been found in control males (the incidence in the control group was originally reported as 0/49 before the reexamination of the slides).

The Agency then requested that additional kidney sections from the mouse study be prepared and examined. The resultant microslides were examined by a number of pathologists. These examinations revealed no additional tumors, but confirmed the presence of the tumors identified in the original study report. The tumor in the control kidney was not present in any of the additional sections.

Because of the equivocal nature of the findings, the Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee asked the expert assistance of the FIFRA Scientific Advisory Panel (SAP) in determining the proper Weight-of-the-Evidence classification of the study. After reviewing all the available evidence, the SAP, in their meeting of February 11-12, 1986, proposed that glyphosate be classified as "Class D," or having "inadequate animal evidence of oncogenicity." The principal reason for this assessment by SAP was their determination that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

Committee's interpretation: In their meeting of June 26, 1991, the Health Effects Carcinogenicity Peer Review Committee concluded that despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females.

c. Nonneoplastic lesions:

Other nonneoplastic changes noted in high-dose male mice included centrilobular hypertrophy and necrosis of hepatocytes, chronic interstitial nephritis, and proximal tubule epithelial cell basophilia and hypertrophy in the kidneys of females. The no-observable-effect level (NOEL) for nonneoplastic chronic effects was the mid-dose level, 5000 ppm.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Glyphosate was tested in this study at levels higher than the limit dose. Body weight gain in males of the high dose was 13, 17 and 27% less than the controls at 3, 12 and 24 months respectively. The decrease in body weight gains was statistically significant ($p < 0.01$). This effect was less obvious in females. The doses tested were considered adequate for the carcinogenic potential assessment of glyphosate.

E. Additional Toxicology Data on Glyphosate

1. Metabolism

When Sprague-Dawley rats were given a single oral dose of C-14 glyphosate, 30 to 36 percent of orally administered glyphosate was absorbed.

Data showed that less than 0.27 percent of the dose was expired as CO_2 within 24 hours. Glyphosate, per se, was the highest radiolabeled material found in the urine and feces. The minimum level of glyphosate extracted from urine and feces was 97.5 percent. Amino methyl phosphonic acid (AMPA) was found in the excreta of animals at levels of 0.2 to 0.3 percent and 0.2 to 0.4 percent in urine and feces, respectively. No detectable AMPA metabolite was found in intravenously dosed rats and high dose, orally dosed rats. There were no other metabolites of glyphosate found.

Based on analysis of radioactivity in urine and feces and using the "sigma-minus" plotting method, males and females had alpha half-lives of 2.11 and 7.52 hours and 5.00 to 6.44 hours, respectively. The beta half-lives of males and females in these groups ranged from 69.0 to 181 hours for males and 79.9 to 337 hours for females.

Less than 1 percent of the absorbed dose remains in tissues and organs, primarily bone. Repeated dosing with glyphosate

does not significantly change the metabolism, distribution, or excretion of glyphosate.

N-Nitrosoglyphosate (NNG)

The Agency has determined that carcinogenicity testing of nitroso contaminants will normally be required only in those cases in which the level of nitroso compounds exceeds 1.0 ppm [see "Pesticide Contaminated with N-nitroso Compounds, proposed policy 45 FR 42854 (June 25, 1980)"]. The levels of NNG in technical glyphosate have been examined by HED. The overall NNG content in individual samples of technical glyphosate analyzed at production plants is shown below:

Samples Analyzed		NNG Observed
No. Samples	Per cent	(ppb)
2035	92.6	< 1000
124	5.6	1000 - 1500
24	1.1	1500 - 2000
13	0.6	2000 - 3000
2	0.1	> 3000

The overall data show that 92.6 percent of the individual glyphosate samples analyzed contain less than 1.0 ppm (1000 ppb) of NNG. TB concluded that the NNG content of glyphosate technical is not toxicologically significant.

2. Mutagenicity

Glyphosate has been tested in several mutagenicity assays and found to be negative in each of the three categories recommended for evaluating genotoxic potential. The acceptable studies include the following: Salmonella assay, both with and without S-9, up to toxicity or 5000 ug/plate, in vivo cytogenetic assay in rat bone marrow up to 1000 mg/kg, mammalian gene HGPRT mutation assay in CHO cells in vitro both with and without S-9 up to toxic levels (10 mg/mL) and rec assay with B. subtilis up to 2000 ug/disk.

Unacceptable studies which were also negative included DNA repair in rat hepatocytes between 0.0000135 and 0.125 mg/ml, and a dominant lethal assay in mice up to 2000 mg/kg.

3. Developmental and Reproductive Toxicity

In rats, doses up to 3500 mg/kg/day showed no evidence of malformations. Evidence of developmental toxicity in the form of unossified sternebrae and decreased fetal body weight was noted in fetuses from the high dose (3500 mg/kg/day). This dose was also toxic to dams as evidenced by weight gain

deficits, altered physical appearance, and mortality during treatment. The developmental and maternal toxic NOEL for this study was 1000 mg/kg/day.

In rabbits, doses up to 350 mg/kg/day showed no evidence of malformations. The highest dose tested was toxic to does as evidenced by altered physical appearance and mortality. No treatment-related developmental effects were noted. The NOEL for maternal toxicity is 175 mg/kg/day and the NOEL for developmental toxicity is 350 mg/kg/day.

In a three-generation reproduction study in the rat, the only toxicologically significant finding was focal renal tubular dilation in the kidneys of male pups from the F_{3b} generation of high-dose dams (30 mg/kg/day). The NOEL for this effect was 10 mg/kg/day. No effects on fertility, reproductive, or other study parameters were noted.

4. Structure - Activity Relationships

Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and reported to be negative.

5. Acute, Subchronic and Chronic Feeding/ Oncogenicity Data

Glyphosate is not considered to be toxic to mammals (rat oral LD_{50} of 4320 mg/kg (both sexes), and a dermal LD_{50} greater than 7940 mg/kg in rabbits).

A 1-year chronic feeding study in dogs at 6/sex/dose was conducted using doses of 0, 20, 100, and 500 mg/kg/day, administered by capsule. The NOEL for the study was 500 mg/kg/day (HDT).

F. Weight of the Evidence Considerations

The Committee considered the following findings to be of significance regarding the weight-of-the-evidence determination of the carcinogenic potential of glyphosate.

1. Glyphosate was associated with increased incidences of pancreatic islet cell adenomas in male Sprague-Dawley rats at all treatment levels in comparison to the concurrent control group (Table 1). Although the low- (18%), mid- (10%) and high-dose group (15%) incidences exceeded the 1.8 to 8.5% range of historical controls from Monsanto's EHL data base, the pancreatic islet cell adenomas were not considered

compound-related for the following reasons: a) there was no statistically significant positive dose-related trend in the occurrence of these tumors or in the incidence of hyperplasia in males over the wide range of dosing (2000 to 20000 ppm), and b) there was no progression to carcinoma. Tertiary evidence from the open literature cited by the registrant showed a range of 0 to 17% for pancreatic islet cell adenomas in Sprague-Dawley male rats for unadjusted data. The incidence of pancreatic islet cell tumors for the two rat studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

No increased incidence of these tumors was observed in female rats in comparision to concurrent controls.

2. C-cell adenomas were slightly increased in male and female mid- and high-dose groups in the rat (Tables 4 and 5). Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

3. There was a slight dose-related increase in hepatocellular adenomas in male rats (Table 7), but the incidence was within the range of historical controls from Monsanto's EHL. This increase was not significant in the pair-wise comparison with controls and there was no progression from adenoma to carcinoma. The incidence of hyperplasia was not compound-related. There were no dose-related increases in the incidences of other hepatocellular lesions. Therefore, the increased incidence of hepatocellular adenomas in males was not considered compound-related.

4. Glyphosate produced an equivocal carcinogenic response in male mice characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

Despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not feel that this lesion was compound-related.

5. Glyphosate was tested up to the limit dose in the rat, and up to levels higher than the limit dose in mice.

6. There was no evidence of genotoxicity for glyphosate.

7. Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and was reported to be negative.

G. <u>Classification</u>:

Considering criteria contained in EPA Guidelines (FR 51:33992-34003, 1986] for classifying a carcinogen, the Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based on lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

END

To: JENKINS, DANIEL J [AG/1920][daniel.j.jenkins@monsanto.com]; Housenger, Jack[Housenger.Jack@epa.gov]; Keigwin, Richard[Keigwin.Richard@epa.gov]; Overstreet, Anne[overstreet.anne@epa.gov]; Rowland, Jess[Rowland.Jess@epa.gov]
From: JENKINS, DANIEL J [AG/1920]
Sent: Fri 3/27/2015 12:35:02 PM
Subject: RE: official german regulator translation of response to IARC

Sorry, for the resend, but please note their statements re EPA

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: JENKINS, DANIEL J [AG/1920]
Sent: Friday, March 27, 2015 8:26 AM
To: Housenger, Jack; 'Keigwin, Richard'; 'Overstreet, Anne'; 'rowland.jess@epa.gov'
Subject: official german regulator translation of response to IARC

FYI

http://www.bfr.bund.de/cm/349/does-glyphosate-cause-cancer.pdf

Dan Jenkins
U.S. Agency Lead

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Office: 202-383-2851

Cell: 571-732-6575

To: Housenger, Jack[Housenger.Jack@epa.gov]
Cc: Strauss, Linda[Strauss.Linda@epa.gov]
From: Jones, Jim
Sent: Tue 3/24/2015 7:37:17 PM
Subject: Re: FW:

Thx. Sharing with Linda. Jim

Sent from my iPhone

On Mar 24, 2015, at 8:57 AM, Housenger, Jack <Housenger.Jack@epa.gov> wrote:

fyi

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, March 24, 2015 10:24 AM
To: JENKINS, DANIEL J [AG/1920]; Goodis, Michael
Cc: Keigwin, Richard; Cyran, Carissa; Rowland, Jess; Anderson, Neil; Housenger, Jack
Subject: RE:

The German Regulators have responded. We hope that EPA would consider the following in their approach to responses:

Does Glyphosate cause cancer?

(English translation of text at http://www.bfr.bund.de/cm/343/loest-glyphosat-krebs-aus.pdf)

Communication 007/2015 BfR March 23, 2015

Glyphosate, the ingredient in plant protection products, was deemed non-carcinogenic after review by national, European and other international institutions including the Joint Meeting on Pesticide Residues of the World Health Organisation and UN Food and Agriculture Organisation, of all the studies at their disposal.

At a meeting of the International Agency for Research on Cancer (IARC) of the World Health Organization in Lyon in March 2015, experts gathered to discuss glyphosate and, based on the studies they looked at, came to a different classification, namely as a Group 2A carcinogen, or "probably" carcinogenic for humans. This Classification was

published in a short report in the journal "Lancet" on March 20, 2015.

The (German) Federal Institute for Risk Assessment (BfR) was appointed EU rapporteur for glyphosate as part of the EU re-evaluation and is commenting on this IARC Classification on the basis of the summary that was published.

Seventeen experts from 11 countries met at the IARC in March 2015 to weigh the carcinogenicity or potential carcinogenicity of four organophosphates and glyphosate, none of which has been classified by the competent European authorities as carcinogenic or mutagenic.

On the basis of the information at the BfR's disposal, the classification of glyphosate in the Lancet on March 20 as belonging to Group 2A (probably carcinogenic to humans) is **scientifically hard to follow and apparently based on very few studies**. The IARC decision cannot be judged definitively, however, since the final IARC Monograph, in which its decision will be backed up with more information, is not yet published.

The recently published IARC classification is based partially on indications of carcinogenic effect in human studies, i.e. a statistical relationship between exposure to glyphosate and an increased risk of non-Hodgkin lymphomas. This risk is derived from three epidemiological studies from the USA, Canada and Sweden. However, this conclusion was not shared a very large scale "Agricultural Health Study", also cited, or by other studies. **In the current report of the BfR to the EU, on the other hand, over 30 epidemiological studies were evaluated. In the comprehensive opinion, there was no proven relationship between exposure to glyphosate and an increased risk of non-Hodgkin's lymphoma or other types of cancer.**

Furthermore, IARC advances findings from animal testing as proof of a carcinogenic effect of glyphosate. All of these findings were also considered in the glyphosate appraisals of the BfR, the EU institutions and the Joint Meeting on Pesticide Residues of the WHO and FAO, which is responsible for the appraisal of pesticide ingredients. These organizations came to the overall conclusion that glyphosate is not carcinogenic. The BfR does not know how many of the 11 long-term studies on rats and mice considered valid by the BfR were available to the IARC.

The theory advanced in one study that skin tumors could be caused by a highly concentrated, irritant formulation with the ingredient were also not regarded by the EU institutions as proof for the carcinogenic qualities of glyphosate.

Indications for a gene toxic potential of glyphosate cannot be concluded from IARC's published summary, since the review also included formulations that were not further described.

The fact that different bodies reach different conclusions from different information and interpretations of experimental data is a daily reality in risk assessment. The BfR will examine IARC'sclassification in detail once the Monograph is published.

Dan Jenkins
U.S. Agency Lead

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Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: JENKINS, DANIEL J [AG/1920]
Sent: Monday, March 23, 2015 10:10 AM
To: 'goodis.michael@epa.gov'
Cc: 'Keigwin, Richard'; 'Cyran, Carissa'; 'rowland.jess@epa.gov'; 'anderson.neil@epa.gov'
Subject:

Mike:

Per our phone conversation. We hope EPA will correct mistakes or absences of fact with respect to its record on glyphosate (including the 2013 statement and the AHS study) as it relates to carcinogenicity.

2009 EPA Glyphosate Reg Review

Carcinogenicity was not identified as a concern in the work plan
http://www.epa.gov/oppsrrd1/registration_review/glyphosate/

2013 Federal Register Notice (FR 25396 Vol. 78, No. 84, Wednesday, May 1, 2013)
Final Rule new tolerances in or on multiple commodities: "EPA has concluded that glyphosate does not pose a cancer risk to humans."

http://www.gpo.gov/fdsys/pkg/FR-2013-05-01/pdf/2013-10316.pdf

"For the herbicide **glyphosate**, there was *limited evidence of carcinogenicity* in humans for non-Hodgkin lymphoma. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals. On the basis of tumours in mice, the United States Environmental Protection Agency (US EPA) originally classified glyphosate as *possibly carcinogenic to humans* (Group C) in 1985. After a re-evaluation of that mouse study, the US EPA changed its classification to *evidence of non-carcinogenicity in humans* (Group E) in 1991. The US EPA Scientific Advisory Panel noted that the re-evaluated glyphosate results were still significant using two statistical tests recommended in the IARC Preamble. The IARC Working Group that conducted the evaluation considered the significant findings from the US EPA report and several more recent positive results in concluding that there is *sufficient evidence of carcinogenicity* in experimental animals. Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby."

http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)70134-8/abstract

http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

Thanks,

Dan Jenkins
U.S. Agency Lead

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1300 I St., NW
Suite 450 East
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Office: 202-383-2851

Cell: 571-732-6575

To: Mojica, Andrea[Mojica.andrea@epa.gov]; Jones, Jim[Jones.Jim@epa.gov]; Keigwin, Richard[Keigwin.Richard@epa.gov]
Cc: Wise, Louise[Wise.Louise@epa.gov]; Perlis, Robert[Perlis.Robert@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]; Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Sisco, Debby[Sisco.Debby@epa.gov]
From: Housenger, Jack
Sent: Tue 5/10/2016 5:31:40 PM
Subject: RE: glyphosate draft response for review

Ex. 5 - Deliberative Process

From: Mojica, Andrea
Sent: Tuesday, May 10, 2016 1:03 PM
To: Jones, Jim <Jones.Jim@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: Housenger, Jack <Housenger.Jack@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: RE: glyphosate draft response for review

Ex. 5 - Deliberative Process

From: Jones, Jim
Sent: Tuesday, May 10, 2016 12:15 PM
To: Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: Housenger, Jack <Housenger.Jack@epa.gov>; Mojica, Andrea <Mojica.andrea@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: Re: glyphosate draft response for review

Thx Rick. Jim

Sent from my iPhone

On May 10, 2016, at 10:48 AM, Keigwin, Richard <Keigwin.Richard@epa.gov> wrote:

Ex. 5 - Deliberative Process

From: Housenger, Jack
Sent: Tuesday, May 10, 2016 10:45 AM
To: Mojica, Andrea <Mojica.andrea@epa.gov>; Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: RE: glyphosate draft response for review

Ex. 5 - Deliberative Process

From: Mojica, Andrea
Sent: Tuesday, May 10, 2016 10:32 AM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Housenger, Jack <Housenger.Jack@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: glyphosate draft response for review

All,

Attached is a draft response to Chairman Lamar Smith's (Committee on Science, Space, and Technology) glyphosate inquiry. I have attached in the incoming letter to the Administrator as well. Please let me know if you have any comments by May 12th.

Thanks,

Andrea

To: Jones, Jim[Jones.Jim@epa.gov]
From: Housenger, Jack
Sent: Thur 11/12/2015 5:33:29 PM
Subject: Re: Glyphosate Efsa review.

I figured you'd want to send it. I'll make sure ord sees.

Sent from my iPhone

On Nov 12, 2015, at 9:08 AM, Jones, Jim <Jones.Jim@epa.gov> wrote:

> I sent to Tom Burke. Could you be sure the technical report gets to the ord team looking at our carc report. Jim
>
> Sent from my iPhone
>
> On Nov 12, 2015, at 7:21 AM, Housenger, Jack <Housenger.Jack@epa.gov> wrote:
>
> > Jim, the Efsa link is below
> > The conclusion is that it is unlikely to be carcinogenic
> >
> > http://www.efsa.europa.eu/en/efsajournal/pub/4302
> >
> > ***Dear Colleagues,***
> >
> > **Today 12 November at 12:00 CET**, EFSA will publish a Conclusion on the Peer review on glyphosate and a complementary technical document.
> >
> > It will be accompanied by a News Story and a non technical summary.
> >
> > The documents are under embargo until **12:00 CET** when they will be published on our website.
> >
> > For any further information on the Conclusion, please contact Jose Tarazona (Jose.Tarazona@efsa.europa.eu).
> >
> > For any further information on the News Story, please contact Simon Terry (simon.terry@efsa.europa.eu).

Best regards,

Djien

Djien Liem, PhD

Lead Expert in International Scientific Cooperation

Advisory Forum and Scientific Cooperation Unit

European Food Safety Authority

Via Carlo Magno 1A

43126 Parma (Italy)

Tel. +39 0521 036225

www.efsa.europa.eu

Sent from my iPhone

To: Rowland, Jess[Rowland.Jess@epa.gov]; Vogel, Dana[Vogel.Dana@epa.gov]; Lowit, Anna[Lowit.Anna@epa.gov]
From: Housenger, Jack
Sent: Tue 9/8/2015 11:27:14 AM
Subject: FW: GLY
Prof_Ivan Rusyn_EN .pdf
Catalogue of Questions - Fragenkatalog Öffentliche Anhörung_EN.pdf

See the note from Ivan below

Ex. 5 - Deliberative Process

From: Rusyn, Ivan [mailto:IRusyn@cvm.tamu.edu]
Sent: Monday, September 07, 2015 3:58 PM
To: Housenger, Jack
Cc: Dix, David
Subject: GLY

Dear Jack,

I hope you had a good summer and had a chance to look through the IARC monograph on glyphosate. Do let me know if there are any questions that you or your staff may have.

As you may know, there is quite a debate in Europe surrounding the BfR draft assessment report on glyphosate renewal. I was asked to appear at the hearings in Bundestag on September 28 (see attached invitation and a list of questions; I diid submit answers and they will be part of the public record after the hearing) and I am trying to catch up on where the government action is on this. I recall Jim Jones saying in an interview published by Reuters that EPA will release its re-assessment in July. Please let me know if that did in fact happen, or whether you have another date.

Also, you may be interested to know that a JMPR Expert Taskforce on Diazinon, Glyphosate and Malathion (http://www.who.int/entity/foodsafety/areas_work/chemical-

risks/etc_final_new_1.pdf?ua=1) conclusions should be released very soon as the group finalized them last week.

Thank you and best regards,

Ivan

Ivan Rusyn, MD, PhD

Professor, Veterinary Integrative Biosciences
Texas A&M University

4458 TAMU

College Station, TX 77843-4458

Office: (979) 458-9866; Cell: (919) 624-2272

PubMed citations

Google Scholar page

http://rusynlab.org

http://comptox.us

List of questions for the hearing on 28 September 2015

1. What is the substantive basis for the different opinions which exist on the question of whether glyphosate is likely to be carcinogenic? How should these differences be viewed and what course of action will now be taken in this regard? What role does the fact that exposure varies depending on directions for use play in assessing the risks?
   What routes of exposure which could lead to an increased risk of cancer are relevant for Germany, with the directions for use currently in application?

2. How do you view the approval of active substances and plant protection products at European Union (EU) level and at national level? Should the existing legal requirement obliging companies applying for approval to make available and finance the necessary scientific studies be changed? And, if so, who should cover the costs? How many scientific studies on the possible carcinogenicity of glyphosate were assessed and did the studies apply to the active substance or to the plant protection product?

3. What alternative plant protection products are available to the agricultural sector to replace glyphosate and what environmental and health impacts would increased use of these products have? What would be the impacts on resistance management if glyphosate were no longer used? What would be the impacts on conservation tillage of replacing glyphosate?

4. What indications of other health hazards posed by glyphosate are you aware of, apart from the probable carcinogenic effects? Which institutions, particularly at international level, are investigating these indications of possible health hazards and what current international research projects assessing the possible health hazards posed by the active substance are you aware of?

5. A significant proportion of studies used by the Federal Institute for Risk Assessment (BfR) are financed or initiated by the chemical industry. What is your opinion of such studies and how do you view their findings?

6. To what extent should the monograph produced by the International Agency for Research on Cancer (IARC) influence the re-authorisation of glyphosate at EU level in your view and to what extent should the precautionary principle be applied regarding authorisation of glyphosate, against the background of studies concluding that glyphosate

is “probably carcinogenic”?

7. What impacts on the health of users, local residents and consumers in your opinion indicate that glyphosate ought not to be used in agriculture?

8. In your view, what impacts on the environment and on agriculture of the active substance glyphosate on the one hand and herbicide-resistant genetically modified plants on the other indicate that glyphosate ought not to be used as an active substance in agriculture?

9. What consequences would a ban on the use of glyphosate have on the agricultural sector in the EU and in countries which export agricultural commodities to the EU?

10. What differences are you aware of regarding the regulations, procedures and criteria applied in assessments by the IARC, Joint Meeting on Pesticide Residues (JMPR), Institute for Risk Assessment (BfR), European Food Safety Authority (EFSA) and, if applicable, the United States Environmental Protection Agency (EPA)? Which regulations may lead to scientific studies not being taken into account and how are the different conclusions reached by these institutions regarding the carcinogenicity of the active substance glyphosate to be viewed against this background?
(If you represent one of the institutions listed above, please indicate this to the *left* of the descriptions of the various regulations, procedures and criteria.)

11. How do you assess the current availability of data regarding the exposure of various groups in the population to glyphosate (with particular reference to professional and non-professional users, residents/bystanders/land users, consumers and children/infants)? In particular, how precisely can the level of (acute and background) exposure be assessed in your view and what (if any) recommendations do you have to improve the availability of data on glyphosate?

12. What consequences would adoption of the IARC classification as "probably carcinogenic to humans" have on the possible new authorisation of glyphosate as an active substance?
(c.f.:
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1272-20150601
p. 152 onwards, Annex 1, 3.6: Carcinogenicity)

Courtesy Translation

Professor Ivan Rusyn, MD
Texas A&M University
College of Veterinary Medicine and
Biomedical Sciences
College Station, Texas 77843
USA

By e-mail to:
IRusyn@cvm.tamu.edu

4 August 2015

Public hearing on Monday, 28 September 2015
List of questions

Dear Professor Rusyn,

Following your invitation from the Chairman of the Committee on Food and Agriculture, Mr Alois Gerig, to attend in an expert capacity the public hearing on the following topic

"Glyphosate: effects on the health of users and consumers, and potential consequences with regard to its approval as a pesticidal active substance"

please find attached the list of questions, as advised.

To allow the Committee members to prepare for the hearing, I would ask you to send your written statements on the twelve questions to the Committee Secretariat by **Wednesday, 9 September 2015,** if possible via e-mail to el-ausschuss@bundestag.de

Yours sincerely,

Margot Heimbach
Committee Secretariat

To: Jones, Jim[Jones.Jim@epa.gov]
From: Housenger, Jack
Sent: Tue 9/8/2015 11:25:41 AM
Subject: FW: GLY
Prof_Ivan Rusyn_EN .pdf
Catalogue of Questions - Fragenkatalog Öffentliche Anhörung_EN.pdf

See the note from Ivan

Ex. 5 - Deliberative Process

From: Rusyn, Ivan [mailto:IRusyn@cvm.tamu.edu]
Sent: Monday, September 07, 2015 3:58 PM
To: Housenger, Jack
Cc: Dix, David
Subject: GLY

Dear Jack,

I hope you had a good summer and had a chance to look through the IARC monograph on glyphosate. Do let me know if there are any questions that you or your staff may have.

As you may know, there is quite a debate in Europe surrounding the BfR draft assessment report on glyphosate renewal. I was asked to appear at the hearings in Bundestag on September 28 (see attached invitation and a list of questions; I diid submit answers and they will be part of the public record after the hearing) and I am trying to catch up on where the government action is on this. I recall Jim Jones saying in an interview published by Reuters that EPA will release its re-assessment in July. Please let me know if that did in fact happen, or whether you have another date.

Also, you may be interested to know that a JMPR Expert Taskforce on Diazinon, Glyphosate and Malathion (http://www.who.int/entity/foodsafety/areas_work/chemical-risks/etc_final_new_1.pdf?ua=1) conclusions should be released very soon as the group finalized them last week.

Thank you and best regards,

Ivan

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PubMed citations

Google Scholar page

http://rusynlab.org

http://comptox.us

List of questions for the hearing on 28 September 2015

1. What is the substantive basis for the different opinions which exist on the question of whether glyphosate is likely to be carcinogenic? How should these differences be viewed and what course of action will now be taken in this regard? What role does the fact that exposure varies depending on directions for use play in assessing the risks?
   What routes of exposure which could lead to an increased risk of cancer are relevant for Germany, with the directions for use currently in application?

2. How do you view the approval of active substances and plant protection products at European Union (EU) level and at national level? Should the existing legal requirement obliging companies applying for approval to make available and finance the necessary scientific studies be changed? And, if so, who should cover the costs? How many scientific studies on the possible carcinogenicity of glyphosate were assessed and did the studies apply to the active substance or to the plant protection product?

3. What alternative plant protection products are available to the agricultural sector to replace glyphosate and what environmental and health impacts would increased use of these products have? What would be the impacts on resistance management if glyphosate were no longer used? What would be the impacts on conservation tillage of replacing glyphosate?

4. What indications of other health hazards posed by glyphosate are you aware of, apart from the probable carcinogenic effects? Which institutions, particularly at international level, are investigating these indications of possible health hazards and what current international research projects assessing the possible health hazards posed by the active substance are you aware of?

5. A significant proportion of studies used by the Federal Institute for Risk Assessment (BfR) are financed or initiated by the chemical industry. What is your opinion of such studies and how do you view their findings?

6. To what extent should the monograph produced by the International Agency for Research on Cancer (IARC) influence the re-authorisation of glyphosate at EU level in your view and to what extent should the precautionary principle be applied regarding authorisation of glyphosate, against the background of studies concluding that glyphosate

is “probably carcinogenic”?

7. What impacts on the health of users, local residents and consumers in your opinion indicate that glyphosate ought not to be used in agriculture?

8. In your view, what impacts on the environment and on agriculture of the active substance glyphosate on the one hand and herbicide-resistant genetically modified plants on the other indicate that glyphosate ought not to be used as an active substance in agriculture?

9. What consequences would a ban on the use of glyphosate have on the agricultural sector in the EU and in countries which export agricultural commodities to the EU?

10. What differences are you aware of regarding the regulations, procedures and criteria applied in assessments by the IARC, Joint Meeting on Pesticide Residues (JMPR), Institute for Risk Assessment (BfR), European Food Safety Authority (EFSA) and, if applicable, the United States Environmental Protection Agency (EPA)? Which regulations may lead to scientific studies not being taken into account and how are the different conclusions reached by these institutions regarding the carcinogenicity of the active substance glyphosate to be viewed against this background?
(If you represent one of the institutions listed above, please indicate this to the *left* of the descriptions of the various regulations, procedures and criteria.)

11. How do you assess the current availability of data regarding the exposure of various groups in the population to glyphosate (with particular reference to professional and non-professional users, residents/bystanders/land users, consumers and children/infants)? In particular, how precisely can the level of (acute and background) exposure be assessed in your view and what (if any) recommendations do you have to improve the availability of data on glyphosate?

12. What consequences would adoption of the IARC classification as "probably carcinogenic to humans" have on the possible new authorisation of glyphosate as an active substance?
(c.f.:
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1272-20150601
p. 152 onwards, Annex 1, 3.6: Carcinogenicity)

Courtesy Translation

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By e-mail to:
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4 August 2015

Public hearing on Monday, 28 September 2015
List of questions

Dear Professor Rusyn,

Following your invitation from the Chairman of the Committee on Food and Agriculture, Mr Alois Gerig, to attend in an expert capacity the public hearing on the following topic

"Glyphosate: effects on the health of users and consumers, and potential consequences with regard to its approval as a pesticidal active substance"

please find attached the list of questions, as advised.

To allow the Committee members to prepare for the hearing, I would ask you to send your written statements on the twelve questions to the Committee Secretariat by **Wednesday, 9 September 2015,** if possible via e-mail to el-ausschuss@bundestag.de

Yours sincerely,

Margot Heimbach
Committee Secretariat

1. Exposure Data

1.1 Identificationof the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 1071-83-6 (acid); also relevant:
38641-94-0 (glyphosate-isopropylamine salt)
40465-66-5 (monoammonium salt)
69254-40-6 (diammoniumsalt)
34494-03-6 (glyphosate-sodium)
81591-81-3 (glyphosate-trimesium)

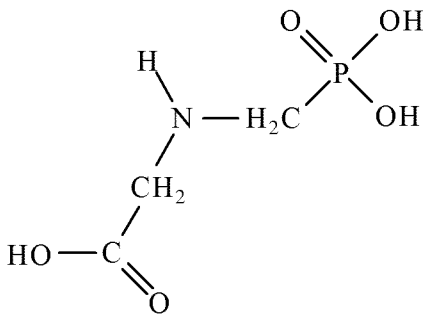
Chem. Abstr. Serv. Name: *N*-(phosphonomethyl)glycine

Preferred IUPAC Name: *N*-(phosphonomethyl)glycine

Synonyms: Gliphosate; glyphosate; glyphosate hydrochloride; glyphosate [calcium, copper (2+), dilithium, disodium, magnesium, monoammonium, monopotassium, monosodium, sodium, or zinc] salt

Trade names: Glyphosate products have been sold worldwide under numerous trade names, including: Abundit Extra; Credit; Xtreme; Glifonox; Glyphogan; Ground-Up; Rodeo; Roundup; Touchdown; Tragli; Wipe Out; Yerbimat (Farm Chemicals International, 2015).

1.1.2 Structural and molecular formulae and relative molecular mass



Molecular formula: $C_3H_8NO_5P$
Relative molecular mass: 169.07

Additional information on chemical structure is also available in the PubChem Compound database (NCBI, 2015).

1.1.3 Chemical and physical properties of the pure substance

Description: Glyphosate acid is a colourless, odourless, crystalline solid. It is formulated as a salt consisting of the deprotonated acid of glyphosate and a cation (isopropylamine, ammonium, or sodium), with more than one salt in some formulations.

Solubility: The acid is of medium solubility at 11.6 g/L in water (at 25 °C) and insoluble in common organic solvents such as acetone, ethanol, and xylene; the alkali-metal and

amine salts are readily soluble in water (Tomlin, 2000).

Volatility: Vapour pressure, 1.31×10^{-2} mPa at 25 °C (negligible) (Tomlin, 2000).

Stability: Glyphosate is stable to hydrolysis in the range of pH 3 to pH 9, and relatively stable to photodegradation (Tomlin, 2000). Glyphosate is not readily hydrolysed or oxidized in the field (Rueppel *et al.* 1977). It decomposes on heating, producing toxic fumes that include nitrogen oxides and phosphorus oxides (IPCS, 2005).

Reactivity: Attacks iron and galvanized steel (IPCS, 2005).

Octanol/water partition coefficient (P): log P, < −3.2 (pH 2–5, 20 °C) (OECD method 107) (Tomlin, 2000).

Henry's law: $< 2.1 \times 10^{-7}$ Pa m^3 mol^{-1} (Tomlin, 2000).

Conversion factor: Assuming normal temperature (25 °C) and pressure (101 kPa), $mg/m^3 = 6.92 \times$ ppm.

1.1.4 Technical products and impurities

Glyphosate is formulated as an isopropylamine, ammonium, or sodium salt in water-soluble concentrates and water-soluble granules. The relevant impurities in glyphosate technical concentrates are formaldehyde (maximum, 1.3 g/kg), *N*-nitrosoglyphosate (maximum, 1 mg/kg), and *N*-nitroso-*N*-phosphonomethylglycine (FAO, 2000). Surfactants and sulfuric and phosphoric acids may be added to formulations of glyphosate, with type and concentration differing by formulation (IPCS, 1994).

1.2 Production and use

1.2.1 Production

(a) Manufacturing processes

Glyphosate was first synthesized in 1950 as a potential pharmaceutical compound, but its herbicidal activity was not discovered until it was re-synthesized and tested in 1970 (Székács & Darvas, 2012). The isopropylamine, sodium, and ammonium salts were introduced in 1974, and the trimesium (trimethylsulfonium) salt was introduced in Spain in 1989. The original patent protection expired outside the USA in 1991, and within the USA in 2000. Thereafter, production expanded to other major agrochemical manufacturers in the USA, Europe, Australia, and elsewhere (including large-scale production in China), but the leading preparation producer remained in the USA (Székács & Darvas, 2012).

There are two dominant families of commercial production of glyphosate, the "alkyl ester" pathways, predominant in China, and the "iminodiacetic acid" pathways, with iminodiacetic acid produced from iminodiacetonitrile (produced from hydrogen cyanide), diethanolamine, or chloroacetic acid (Dill *et al.*, 2010; Tian *et al.*, 2012).

To increase the solubility of technical-grade glyphosate acid in water, it is formulated as its isopropylamine, monoammonium, potassium, sodium, or trimesium salts. Most common is the isopropylamine salt, which is formulated as a liquid concentrate (active ingredient, 5.0–62%), ready-to-use liquid (active ingredient, 0.5–20%), pressurized liquid (active ingredient, 0.75–0.96%), solid (active ingredient, 76–94%), or pellet/tablet (active ingredient, 60–83%) (EPA, 1993a).

There are reportedly more than 750 products containing glyphosate for sale in the USA alone (NPIC, 2010). Formulated products contain various non-ionic surfactants, most notably polyethyloxylated tallowamine (POEA), to

facilitate uptake by plants (Székács & Darvas, 2012). Formulations might contain other active ingredients, such as simasine, 2,4-dichlorophenoxyacetic acid (2,4-D), or 4-chloro-2-methylphenoxyacetic acid (IPCS, 1996), with herbicide resistance driving demand for new herbicide formulations containing multiple active ingredients (Freedonia, 2012).

(b) Production volume

Glyphosate is reported to be manufactured by at least 91 producers in 20 countries, including 53 in China, 9 in India, 5 in the USA, and others in Australia, Canada, Cyprus, Egypt, Germany, Guatemala, Hungary, Israel, Malaysia, Mexico, Singapore, Spain, Taiwan (China), Thailand, Turkey, the United Kingdom, and Venezuela (Farm Chemicals International, 2015). Glyphosate was registered in over 130 countries as of 2010 and is probably the most heavily used herbicide in the world, with an annual global production volume estimated at approximately 600 000 tonnes in 2008, rising to about 650 000 tonnes in 2011, and to 720 000 tonnes in 2012 (Dill *et al.*, 2010; CCM International, 2011; Hilton, 2012; Transparency Market Research, 2014).

Production and use of glyphosate have risen dramatically due to the expiry of patent protection (see above), with increased promotion of non-till agriculture, and with the introduction in 1996 of genetically modified glyphosate-tolerant crop varieties (Székács & Darvas, 2012). In the USA alone, more than 80 000 tonnes of glyphosate were used in 2007 (rising from less than 4000 tonnes in 1987) (EPA, 1997, 2011). This rapid growth rate was also observed in Asia, which accounted for 30% of world demand for glyphosate in 2012 (Transparency Market Research, 2014). In India, production increased from 308 tonnes in 2003–2004, to 2100 tonnes in 2007–2008 (Ministry of Chemicals & Fertilizers, 2008). China currently produces more than 40% of the global supply of glyphosate, exports almost 35% of the global supply (Hilton, 2012), and reportedly has sufficient production capacity to satisfy total global demand (Yin, 2011).

1.2.2 Uses

Glyphosate is a broad-spectrum, post-emergent, non-selective, systemic herbicide, which effectively kills or suppresses all plant types, including grasses, perennials, vines, shrubs, and trees. When applied at lower rates, glyphosate is a plant-growth regulator and desiccant. It has agricultural and non-agricultural uses throughout the world.

(a) Agriculture

Glyphosate is effective against more than 100 annual broadleaf weed and grass species, and more than 60 perennial weed species (Dill *et al.*, 2010). Application rates are about 1.5–2 kg/ha for pre-harvest, post-planting, and pre-emergence use; about 4.3 kg/ha as a directed spray in vines, orchards, pastures, forestry, and industrial weed control; and about 2 kg/ha as an aquatic herbicide (Tomlin, 2000). Common application methods include broadcast, aerial, spot, and directed spray applications (EPA, 1993a).

Due to its broad-spectrum activity, the use of glyphosate in agriculture was formerly limited to post-harvest treatments and weed control between established rows of tree, nut, and vine crops. Widespread adoption of no-till and conservation-till practices (which require chemical weed control while reducing soil erosion and labour and fuel costs) and the introduction of transgenic crop varieties engineered to be resistant to glyphosate have transformed glyphosate to a post-emergent, selective herbicide for use on annual crops (Duke & Powles, 2009; Dill *et al.* 2010). Glyphosate-resistant transgenic varieties have been widely adopted for the production of corn, cotton, canola, and soybean (Duke & Powles, 2009). Production of such crops accounted for 45% of worldwide demand for glyphosate in 2012 (Transparency Market Research, 2014). However, in Europe,

where the planting of genetically modified crops has been largely restricted, post-harvest treatment is still the most common application of glyphosate (Glyphosate Task Force, 2014). Intense and continuous use of glyphosate has led to the emergence of resistant weeds that may reduce its effectiveness (Duke & Powles, 2009).

(b) Residential use

Glyphosate is widely used for household weed control throughout the world. In the USA, glyphosate was consistently ranked as the second most commonly used pesticide (after 2,4-D) in the home and garden market sector between 2001 and 2007, with an annual use of 2000–4000 tonnes (EPA, 2011).

(c) Other uses

Glyphosate was initially used to control perennial weeds on ditch banks and roadsides and under power lines (Dill *et al.*, 2010). It is also used to control invasive species in aquatic or wetland systems (Tu *et al.*, 2001). Approximately 1–2% of total glyphosate use in the USA is in forest management (Mance, 2012).

Glyphosate has been used in a large-scale aerial herbicide-spraying programme begun in 2000 to reduce the production of cocaine in Colombia (Lubick, 2009), and of marijuana in Mexico and South America (Székács & Darvas, 2012).

(d) Regulation

Glyphosate has been registered for use in at least 130 countries (Dill *et al.*, 2010). In the USA, all uses are eligible for registration on the basis of a finding that glyphosate "does not pose unreasonable risks or adverse effects to humans or the environment" (EPA, 1993a). A review conducted in 2001 in connection with the registration process in the European Union reached similar conclusions regarding animal and human safety, although the protection of groundwater during non-crop use was identified as requiring particular attention in the short term (European Commission, 2002).

Nevertheless, as worldwide rates of adoption of herbicide-resistant crops and of glyphosate use have risen in recent years (Duke & Powles, 2009), restriction of glyphosate use has been enacted or proposed in several countries, although documented actions are few. In 2013, the Legislative Assembly of El Salvador voted a ban on the use of pesticides containing glyphosate (República de El Salvador, 2013). Sri Lanka is reported to have instituted a partial ban based on an increasing number of cases of chronic kidney disease among agricultural workers, but the ban was lifted after 2 months (ColomboPage, 2014). The reasons for such actions have included the development of resistance among weed species, as well as health concerns.

No limits for occupational exposure were identified by the Working Group.

1.3 Measurement and analysis

Several methods exist for the measurement of glyphosate and its major metabolite aminomethyl phosphonic acid (AMPA) in various media, including air, water, urine, and serum (Table 1.1). The methods largely involve derivatization with 9-fluorenylmethyl chloro formate (FMOC-Cl) to reach sufficient retention in chromatographic columns (Kuang *et al.*, 2011; Botero-Coy *et al.*, 2013). Chromatographic techniques that do not require derivatization and enzyme-linked immunosorbent assays (ELISA) are under development (Sanchís *et al.*, 2012).

Table 1.1 Methods for the analysis of glyphosate

Sample matrix	Assay procedure	Limit of detection	Reference
Water	HPLC/MS (with online solid-phase extraction)	0.08 µg/L	Lee *et al.* (2001)
	ELISA	0.05 µg/L	Abraxis (2005)
	LC-LC-FD	0.02 µg/L	Hidalgo *et al.* (2004)
	Post HPLC column derivatization and FD	6.0 µg/L	EPA (1992)
	UV visible spectrophotometer (at 435 ng)	1.1 µg/L	Jan *et al.* (2009)
Soil	LC–MS/MS with triple quadrupole	0.02 mg/kg	Botero-Coy *et al.* (2013)
Dust	GC-MS-MID	0.0007 mg/kg	Curwin *et al.* (2005)
Air	HPLC/MS with online solid-phase extraction	0.01 ng/m^3	Chang *et al.* (2011)
Fruits and vegetables	HILIC/WAX with ESI-MS/MS	1.2 µg/kg	Chen *et al.* (2013)
Field crops (rice, maize and soybean)	LC–ESI-MS/MS	0.007–0.12 mg/kg	Botero-Coy *et al.* (2013b)
Plant vegetation	HPLC with single polymeric amino column	0.3 mg/kg	Nedelkoska & Low (2004)
Serum	LC–MS/MS	0.03 µg/mL 0.02 µg/mL (aminomethylphosphonic acid) 0.01 µg/mL (3-methylphosphinicopropionic acid)	Yoshioka *et al.* (2011)
Urine	HPLC with post-column reaction and FD	1 µg/L	Acquavella *et al.* (2004)
	ELISA	0.9 µg/L	Curwin *et al.* (2007)

ELISA, enzyme-linked immunosorbent assay; ESI-MS/MS, electrospray tandem mass spectrometry; FD, fluorescence detection; GC-MS-MID, gas chromatography-mass spectrometry in multiple ion detection mode; HILIC/WAX, hydrophilic interaction/weak anion-exchange liquid chromatography; HPLC/MS, high-performance liquid chromatography with mass spectrometry; HPLC, high-performance liquid chromatography; LC-ESI–MS/MS, liquid chromatography-electrospray–tandem mass spectrometry; LC–LC, coupled-column liquid chromatography; LC–MS/MS, liquid chromatography–tandem mass spectrometry

1.4 Occurrence and exposure

1.4.1 Exposure

(a) Occupational exposure

Studies related to occupational exposure to glyphosate have included farmers and tree nursery workers in the USA, forestry workers in Canada and Finland, and municipal weed-control workers in the United Kingdom (Centre de Toxicologie du Québec, 1988; Jauhiainen *et al.*, 1991; Lavy *et al.*, 1992; Acquavella *et al.*, 2004; Johnson *et al.*, 2005). Para-occupational exposures to glyphosate have also been measured in farming families (Acquavella *et al.*, 2004; Curwin *et al.*, 2007). These studies are summarized in Table 1.2.

(b) Community exposure

Glyphosate can be found in soil, air, surface water, and groundwater (EPA, 1993a). Once in the environment, glyphosate is adsorbed to soil and is broken down by soil microbes to AMPA (Borggaard & Gimsing, 2008). In surface water, glyphosate is not readily broken down by water or sunlight (EPA, 1993a). Despite extensive worldwide use, there are relatively few studies

Table 1.2 Occupational and para-occupational exposure to glyphosate

Industry, country, year	Job/process	Results	Comments/additional data	Reference
Forestry				
Canada, 1986		Arithmetic mean of air glyphosate concentrations:	Air concentrations of glyphosate were measured at the work sites of one crew (five workers) during ground spraying 268 urine samples were collected from 40 workers; glyphosate concentration was above the LOD (15 µg/L) in 14%	Centre de Toxicologie du Québec (1988)
	Signaller	Morning, 0.63 µg/m^3 Afternoon, 2.25 µg/m^3		
	Operator	Morning, 1.43 µg/m^3 Afternoon, 6.49 µg/m^3		
	Overseer	Morning, 0.84 µg/m^3 Afternoon, 2.41 µg/m^3		
	Mixer	Morning, 5.15 µg/m^3 Afternoon, 5.48 µg/m^3		
Finland, year NR	Workers performing silvicultural clearing (n = 5)	Range of air glyphosate concentrations, < 1.25–15.7 µg/m^3 (mean, NR)	Clearing work was done with brush saws equipped with pressurized herbicide sprayers Air samples were taken from the workers' breathing zone (number of samples, NR) Urine samples were collected during the afternoons of the working week (number, NR) Glyphosate concentrations in urine were below the LOD (10 µg/L)	Jauhiainen *et al.* (1991)
USA, year NR	Workers in two tree nurseries (n = 14)	In dermal sampling, 1 of 78 dislodgeable residue samples were positive for glyphosate The body portions receiving the highest exposure were ankles and thighs	Dermal exposure was assessed with gauze patches attached to the clothing and hand rinsing Analysis of daily urine samples repeated over 12 weeks was negative for glyphosate	Lavy *et al.* (1992)
Weed control				
United Kingdom, year NR	Municipal weed control workers (n = 18)	Median, 16 mg/m^3 in 85% of 21 personal air samples for workers spraying with mechanized all-terrain vehicle Median, 0.12 mg/m^3 in 33% of 12 personal air samples collected from workers with backpack with lance applications	[The Working Group noted that the reported air concentrations were substantially higher than in other studies, but was unable to confirm whether the data were for glyphosate or total spray fluid] Dermal exposure was also measured, but reported as total spray fluid, rather than glyphosate	Johnson *et al.* (2005)

Table 1.2 (continued)

Industry, country, year	Job/process	Results	Comments/additional data	Reference
Farming				
USA, 2001	Occupational and para-occupational exposure of 24 farm families (24 fathers, 24 mothers and 65 children). Comparison group: 25 non-farm families (23 fathers, 24 mothers and 51 children)	Geometric mean (range) of glyphosate concentrations in urine: Non-farm fathers, 1.4 µg/L (0.13–5.4) Farm fathers, 1.9 µg/L (0.02–18) Non-farm mothers, 1.2 µg/L (0.06–5.0) Farm mothers, 1.5 µg/L (0.10–11) Non-farm children, 2.7 µg/L (0.10–9.4) Farm children, 2.0 µg/L (0.02–18)	Frequency of glyphosate detection ranged from 66% to 88% of samples (observed concentrations below the LOD were not censored). Detection frequency and geometric mean concentration were not significantly different between farm and non-farm families (observed concentrations below the LOD were not censored)	Curwin et al. (2007)
USA, year NR	Occupational and para-occupational exposures of 48 farmers, their spouses, and 79 children	Geometric mean (range) of glyphosate concentration in urine on day of application: Farmers, 3.2 µg/L (< 1 to 233 µg/L) Spouses, NR (< 1 to 3 µg/L) Children, NR (< 1 to 29 µg/L)	24-hour composite urine samples for each family member the day before, the day of, and for 3 days after a glyphosate application. Glyphosate was detected in 60% of farmers' samples, 4% of spouses' samples and 12% of children's samples the day of spraying and in 27% of farmers' samples, 2% of spouses' samples and 5% of children's samples 3 days after	Acquavella et al. (2004)

LOD, limit of detection; ND, not detected; NR, not reported

on the environmental occurrence of glyphosate (Kolpin *et al.*, 2006).

(i) Air

Very few studies of glyphosate in air were available to the Working Group. Air and rain-water samples were collected during two growing seasons in agricultural areas in Indiana, Mississippi, and Iowa, USA (Chang *et al.*, 2011). The frequency of glyphosate detection ranged from 60% to 100% in air and rain samples, and concentrations ranged from < 0.01 to 9.1 ng/m^3 in air samples and from < 0.1 to 2.5 µg/L in rainwater samples. Atmospheric deposition was measured at three sites in Alberta, Canada. Rainfall and particulate matter were collected as total deposition at 7-day intervals throughout the growing season. Glyphosate deposition rates ranged from < 0.01 to 1.51 µg/m^2 per day (Humphries *et al.*, 2005).

No data were available to the Working Group regarding glyphosate concentrations in indoor air.

(ii) Water

Glyphosate in the soil can leach into ground-water, although the rate of leaching is believed to be low (Borggaard & Gimsing, 2008; Simonsen *et al.*, 2008). It can also reach surface waters by direct emission, atmospheric deposition, and by adsorption to soil particles suspended in runoff water (EPA, 1993a; Humphries *et al.*, 2005). Table 1.3 summarizes data on concentrations of glyphosate or AMPA in surface water and groundwater.

(iii) Residues in food and dietary intake

Glyphosate residues have been measured in cereals, fruits, and vegetables (Table 1.4). Residues were detected in 0.04% of 74 305 samples of fruits, vegetables, and cereals tested from 27 member states of the European Union, and from Norway, and Iceland in 2007 (EFSA, 2009). In cereals, residues were detected in 50% of samples tested in Denmark in 1998–1999, and in 9.5% of samples tested from member states of the European Union, and from Norway and Iceland in 2007 (Granby & Vahl, 2001; EFSA, 2009). In the United Kingdom, food sampling for glyphosate residues has concentrated mainly on cereals, including bread and flour. Glyphosate has been detected regularly and usually below the reporting limit (Pesticide Residues Committee, 2007, 2008, 2009, 2010). Six out of eight samples of tofu made from Brazilian soy contained glyphosate, with the highest level registered being 1.1 mg/kg (Pesticide Residues Committee, 2007).

(iv) Household exposure

In a survey of 246 California households, 14% were found to possess at least one product containing glyphosate (Guha *et al.*, 2013).

(v) Biological markers

Glyphosate concentrations in urine were analysed in urban populations in Europe, and in a rural population living near areas sprayed for drug eradication in Colombia (MLHB, 2013; Varona *et al.*, 2009). Glyphosate concentrations in Colombia were considerably higher than in Europe, with means of 7.6 ng/L and 0.02 µg/L, respectively (Table 1.5). In a study in Canada, glyphosate concentrations in serum ranged from undetectable to 93.6 ng/mL in non-pregnant women (n = 39), and were undetectable in serum of pregnant women (n = 30) and fetal cord serum (Aris & Leblanc, 2011).

1.4.2 Exposure assessment

Exposure assessment methods in epidemiological studies on glyphosate and cancer are discussed in Section 2.0 of the *Monograph* on Malathion, in the present volume.

Table 1.3 Concentration of glyphosate and AMPA in water

Country, year of sampling	Number of samples/setting	Results	Comments/additional data	Reference
USA, 2002	51 streams/agricultural areas (154 samples)	Maximum glyphosate concentration, 5.1 µg/L Maximum AMPA concentration, 3.67 µg/L	The samples were taken following pre- and post-emergence application and during harvest season Glyphosate detected in 36% of samples; AMPA detected in 69% of samples	Battaglin *et al.* (2005)
USA, 2002	10 wastewater treatment plants and two reference streams (40 samples)	Glyphosate, range ≤ 0.1–2 µg/L AMPA, range ≤ 0.1–4 µg/L	AMPA was detected more frequently (67.5%) than glyphosate (17.5%)	Kolpin *et al.* (2006)
Canada, 2002	3 wetlands and 10 agricultural streams (74 samples)	Range, < 0.02–6.08 µg/L	Glyphosate was detected in most of the wetlands and streams (22% of samples)	Humphries *et al.* (2005)
Colombia, year NR	5 areas near crops and coca eradication (24 samples)	Maximum concentration, 30.1 µg/L (minimum and mean, NR)	Glyphosate detected in 8% of samples (MDL, 25 µg/L)	Solomon *et al.* (2007)
Denmark, 2010–2012	4 agricultural sites (450 samples)	Range, < 0.1–31.0 µg/L	Glyphosate detected in 23% of samples; AMPA detected in 25% of samples	Brüch *et al.* (2013)

AMPA, aminomethylphosphonic acid; MDL, method detection limit; NR, data not reported

Table 1.4 Concentrations of glyphosate in food

Country, year	Type of food	Results	Comments/additional data	Reference
Denmark, 1998, 1999	Cereals	> 50% of samples had detectable residues Means: 0.08 mg/kg in 1999 and 0.11 mg/kg in 1998	49 samples of the 1998 harvest 46 samples of the 1999 harvest	Granby & Vahl (2001)
27 European Union member states, Norway and Iceland, 2007	350 different food commodities	0.04% of 2302 fruit, vegetable and cereal samples 9.5% of 409 cereal samples	74 305 total samples	EFSA (2009)
Australia, 2006	Composite sample of foods consumed in 24 hours	75% of samples had detectable residues Mean, 0.08 mg/kg Range, < 0.005 to 0.5 mg/kg	20 total samples from 43 pregnant women	McQueen *et al.* (2012)

Table 1.5 Concentrations of glyphosate and AMPA in urine and serum in the general population

Country, period	Subjects	Results	Comments/additional data	Reference
Urine				
18 European countries, 2013	162 individuals	Arithmetic mean of glyphosate concentration: 0.21 µg/L (maximum, 1.56 µg/L) Arithmetic mean of AMPA concentration: 0.19 µg/L (maximum, 2.63 µg/L)	44% of samples had quantifiable levels of glyphosate and 36% had quantifiable levels of AMPA	Mörlein (2015)
Colombia, 2005–2006	112 residents of areas sprayed for drug eradication	Arithmetic mean (range) of glyphosate concentration: 7.6 µg/L (ND–130 µg/L) Arithmetic mean (range) of AMPA concentration: 1.6 µg/L (ND–56 µg/L)	40% of samples had detectable levels of glyphosate and 4% had detectable levels of AMPA (LODs, 0.5 and 1.0 µg/L, respectively) Urinary glyphosate was associated with use in agriculture	Varona *et al.* (2009)
Serum				
Canada, NR	30 pregnant women and 39 non-pregnant women	ND in serum of pregnant women or cord serum; Arithmetic mean, 73.6 µg/L, (range, ND–93.6 µg/L) in non-pregnant women	No subject had worked or lived with a spouse working in contact with pesticides LOD, 15 µg/L	Aris & Leblanc (2011)

AMPA, aminomethylphosphonic acid; LOD, limit of detection; ND, not detected; NR, not reported

2. Cancer in Humans

2.0 General discussion of epidemiological studies

A general discussion of the epidemiological studies on agents considered in Volume 112 of the *IARC Monographs* is presented in Section 2.0 of the *Monograph* on Malathion.

2.1 Cohort studies

See Table 2.1

The Agricultural Health Study (AHS), a large prospective cohort study conducted in Iowa and North Carolina in the USA, is the only cohort study to date to have published findings on exposure to glyphosate and the risk of cancer at many different sites (Alavanja *et al.*, 1996; NIH, 2015) (see Section 2.0 of the *Monograph* on Malathion, in the present volume, for a detailed description of this study).

The enrolment questionnaire from the AHS sought information on the use of 50 pesticides (ever or never exposure), crops grown and livestock raised, personal protective equipment used, pesticide application methods used, other agricultural activities and exposures, nonfarm occupational exposures, and several lifestyle, medical, and dietary variables. The duration (years) and frequency (days per year) of use was investigated for 22 of the 50 pesticides in the enrolment questionnaire. [Blair *et al.* (2011) assessed the possible impact of misclassification of occupational pesticide exposure on relative risks, demonstrating that nondifferential exposure misclassification biases relative risk estimates towards the null in the AHS and tends to decrease the study power.]

The first report of cancer incidence associated with pesticide use in the AHS cohort considered cancer of the prostate (Alavanja *et al.*, 2003). Risk estimates for exposure to glyphosate were not presented, but no significant exposure–response association with cancer of the prostate was found. In an updated analysis of the AHS (1993 to 2001), De Roos *et al.* (2005a) (see below) also found no association between exposure to glyphosate and cancer of the prostate (relative risk, RR, 1.1; 95% CI, 0.9–1.3) and no exposure–response trend (*P* value for trend = 0.69).

De Roos *et al.* (2005a) also evaluated associations between exposure to glyphosate and the incidence of cancer at several other sites. The prevalence of ever-use of glyphosate was 75.5% (> 97% of users were men). In this analysis, exposure to glyphosate was defined as: (a) ever personally mixed or applied products containing glyphosate; (b) cumulative lifetime days of use, or "cumulative exposure days" (years of use × days/year); and (c) intensity-weighted cumulative exposure days (years of use × days/year × estimated intensity level). Poisson regression was used to estimate exposure–response relations between exposure to glyphosate and incidence of all cancers combined, and incidence of 12 cancer types: lung, melanoma, multiple myeloma, and non-Hodgkin lymphoma (see Table 2.1) as well as oral cavity, colon, rectum, pancreas, kidney, bladder, prostate, and leukaemia (results not tabulated). Exposure to glyphosate was not associated with all cancers combined (RR, 1.0; 95% CI, 0.9–1.2; 2088 cases). For multiple myeloma, the relative risk was 1.1 (95% CI, 0.5–2.4; 32 cases) when adjusted for age, but was 2.6 (95% CI, 0.7–9.4) when adjusted for multiple confounders (age, smoking, other pesticides, alcohol consumption, family history of cancer, and education); in analyses by cumulative exposure-days and intensity-weighted exposure-days, the relative risks were around 2.0 in the highest tertiles. Furthermore, the association between multiple myeloma and exposure to glyphosate only appeared within the subgroup for which complete data were available on all the covariates; even without any adjustment, the risk of multiple myeloma associated with glyphosate use was increased by twofold among the smaller subgroup with available covariate data

Table 2.1 Cohort studies of cancer and exposure to glyphosate

Reference, study location, enrolment period/follow-up, study-design	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
De Roos *et al.* (2005a) Iowa and North Carolina, USA 1993–2001	54 315 (after exclusions, from a total cohort of 57 311) licensed pesticide applicators Exposure assessment method: questionnaire; semi-quantitative assessment from self-administered questionnaire	Lung	Ever use	147	0.9 (0.6–1.3)	Age, smoking, other pesticides, alcohol consumption, family history of cancer, education	AHS Cancer sites investigated: lung, melanoma, multiple myeloma and NHL (results tabulated) as well as oral cavity, colon, rectum, pancreas, kidney, bladder, prostate and leukaemia (results not tabulated) [Strengths: large cohort; specific assessment of glyphosate, semiquantitative exposure assessment. Limitations: risk estimates based on self-reported exposure; limited to licensed applicators; potential exposure to multiple pesticides]
			Cumulative exposure days:				
			1–20	40	1 (ref.)		
			21–56	26	0.9 (0.5–1.5)		
			57–2678	26	0.7 (0.4–1.2)		
			Trend-test *P* value: 0.21				
		Melanoma	Ever use	75	1.6 (0.8–3)		
			1–20	23	1 (ref.)		
			21–56	20	1.2 (0.7–2.3)		
			57–2678	14	0.9 (0.5–1.8)		
			Trend-test *P* value: 0.77				
		Multiple myeloma	Ever use	32	1.1 (0.5–2.4)	Age only (results in this row only)	
			Ever use	32	2.6 (0.7–9.4)		
			1–20	8	1 (ref.)		
			21–56	5	1.1 (0.4–3.5)		
			Trend-test *P* value: 0.27				
		NHL	Ever use	92	1.1 (0.7–1.9)		
			1–20	29	1 (ref.)		
			21–56	15	0.7 (0.4–1.4)		
			57–2678	17	0.9 (0.5–1.6)		
			Trend-test *P* value: 0.73				

Table 2.1 (continued)

Reference, study location, enrolment period/follow-up, study-design	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Flower *et al.* (2004) Iowa and North Carolina, USA Enrolment, 1993–1997; follow-up, 1975–1998	21 375; children (aged < 19 years) of licensed pesticide applicators in Iowa (*n* = 17 357) and North Carolina (*n* = 4018) Exposure assessment method: questionnaire	Childhood cancer	Maternal use of glyphosate (ever) Paternal use of glyphosate (prenatal)	13 6	0.61 (0.32–1.16) 0.84 (0.35–2.34)	Child's age at enrolment	AHS Glyphosate results relate to the Iowa participants only [Strengths: Large cohort; specific assessment of glyphosate. Limitations: based on self-reported exposure; potential exposure to multiple pesticides; limited power for glyphosate exposure]
Engel *et al.* (2005) Iowa and North Carolina, USA Enrolment, 1993–1997 follow-up to 2000	30 454 wives of licensed pesticide applicators with no history of breast cancer at enrolment Exposure assessment method: questionnaire	Breast	Direct exposure to glyphosate Husband's use of glyphosate	82 109	0.9 (0.7–1.1) 1.3 (0.8–1.9)	Age, race, state	AHS [Strengths: large cohort; specific assessment of glyphosate. Limitations: based on self-reported exposure; limited to licensed applicators; potential exposure to multiple pesticides]
Lee *et al.* (2007) Iowa and North Carolina, USA Enrolment, 1993–1997; follow-up to 2002	56 813 licensed pesticide applicators Exposure assessment method: questionnaire	Colorectum Colon Rectum	Exposed to glyphosate Exposed to glyphosate Exposed to glyphosate	225 151 74	1.2 (0.9–1.6)	Age, smoking, state, total days of any pesticide application	AHS [Strengths: large cohort. Limitations: based on self-reported exposure, limited to licensed applicators, potential

Table 2.1 (continued)

Reference, study location, enrolment period/follow-up, study-design	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Andreotti et al. (2009) Iowa and North Carolina, USA Enrolment, 1993–1997; follow-up to 2004 Nested case–control study	Cases: 93 (response rate, NR); identified from population-based state-cancer registries. Incident cases diagnosed between enrolment and 31 December 2004 (> 9 years follow-up) included in the analysis. Participants with any type of prevalent cancer at enrolment were excluded. Vital status was obtained from the state death registries and the National Death Index. Participants who left North Carolina or Iowa were not subsequently followed for cancer occurrence. Controls: 82 503 (response rate, NR); cancer-free participants enrolled in the cohort Exposure assessment method: questionnaire providing detailed pesticide use, demographic and lifestyle information. Ever-use of 24 pesticides and intensity-weighted lifetime days [(lifetime exposure days) × (exposure intensity score)] of 13 pesticides was assessed	Pancreas (C25.0–C25.9)	Ever exposure to glyphosate Low (< 185 days) High (≥ 185 days) Trend-test *P* value: 0.85	55 29 19	1.1 (0.6–1.7)	Age, smoking, diabetes	AHS [Strengths: large cohort. Limitations: based on self-reported exposure; limited to licensed applicators; potential exposure to multiple pesticides]

AHS, Agricultural Health Study; NHL, non-Hodgkin lymphoma; NR, not reported

(De Roos *et al.*, 2005b). [The study had limited power for the analysis of multiple myeloma; there were missing data on covariates when multiple adjustments were done, limiting the interpretation of the findings.] A re-analysis of these data conducted by Sorahan (2015) confirmed that the excess risk of multiple myeloma was present only in the subset with no missing information (of 22 cases in the restricted data set). In a subsequent cross-sectional analysis of 678 male participants from the same cohort, Landgren *et al.* (2009) did not find an association between exposure to glyphosate and risk of monoclonal gammopathy of undetermined significance (MGUS), a pre-malignant plasma disorder that often precedes multiple myeloma (odds ratio, OR, 0.5; 95% CI, 0.2–1.0; 27 exposed cases).

Flower *et al.* (2004) reported the results of the analyses of risk of childhood cancer associated with pesticide application by parents in the AHS. The analyses for glyphosate were conducted among 17 357 children of Iowa pesticide applicators from the AHS. Parents provided data via questionnaires (1993–1997) and the cancer follow-up (retrospectively and prospectively) was done through the state cancer registries. Fifty incident childhood cancers were identified (1975–1998; age, 0–19 years). For all the children of the pesticide applicators, risk was increased for all childhood cancers combined, for all lymphomas combined, and for Hodgkin lymphoma, compared with the general population. The odds ratio for use of glyphosate and risk of childhood cancer was 0.61 (95% CI, 0.32–1.16; 13 exposed cases) for maternal use and 0.84 (95% CI, 0.35–2.34; 6 exposed cases) for paternal use. [The Working Group noted that this analysis had limited power to study a rare disease such as childhood cancer.]

Engel *et al.* (2005) reported on incidence of cancer of the breast among farmers' wives in the AHS cohort, which included 30 454 women with no history of cancer of the breast before enrolment in 1993–1997. Information on pesticide use and other factors was obtained at enrolment by self-administered questionnaire from the women and their husbands. A total of 309 incident cases of cancer of the breast were identified until 2000. There was no difference in incidence of cancer of the breast for women who reported ever applying pesticides compared with the general population. The relative risk for cancer of the breast among women who had personally used glyphosate was 0.9 (95% CI, 0.7–1.1; 82 cases) and 1.3 (95% CI, 0.8–1.9; 109 cases) among women who never used pesticides but whose husband had used glyphosate. [No information on duration of glyphosate use by the husband was presented.] Results for glyphosate were not further stratified by menopausal status.

Lee *et al.* (2007) investigated the relationship between exposure to agricultural pesticides and incidence of cancer of the colorectum in the AHS. A total of 56 813 pesticide applicators with no prior history of cancer of the colorectum were included in this analysis, and 305 incident cancers of the colorectum (colon, 212; rectum, 93) were diagnosed during the study period, 1993–2002. Most of the 50 pesticides studied were not associated with risk of cancer of the colorectum, and the relative risks with exposure to glyphosate were 1.2 (95% CI, 0.9–1.6), 1.0 (95% CI, 0.7–1.5), and 1.6 (95% CI, 0.9–2.9) for cancers of the colorectum, colon, and rectum, respectively.

Andreotti *et al.* (2009) examined associations between the use of pesticides and cancer of the pancreas using a case–control analysis nested in the AHS. This analysis included 93 incident cases of cancer of the pancreas (64 applicators, 29 spouses) and 82 503 cancer-free controls who completed the enrolment questionnaire. Ever-use of 24 pesticides and intensity-weighted lifetime days [(lifetime exposure days) × (exposure intensity score)] of 13 pesticides were assessed. Risk estimates were calculated controlling for age, smoking, and diabetes. The odds ratio for ever- versus never-exposure to glyphosate was

1.1 (95% CI, 0.6–1.7; 55 exposed cases), while the odds ratio for the highest category of level of intensity-weighted lifetime days was 1.2 (95% CI, 0.6–2.6; 19 exposed cases).

Dennis *et al.* (2010) reported that exposure to glyphosate was not associated with cutaneous melanoma within the AHS. [The authors did not report a risk estimate.]

2.2 Case–control studies on non-Hodgkin lymphoma, multiple myeloma, and leukaemia

2.2.1 Non-Hodgkin lymphoma

See Table 2.2

(a) Case–control studies in the midwest USA

Cantor *et al.* (1992) conducted a case–control study of incident non-Hodgkin lymphoma (NHL) among males in Iowa and Minnesota, USA (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). A total of 622 white men and 1245 population-based controls were interviewed in person. The association with farming occupation and specific agricultural exposures were evaluated. When compared with non-farmers, the odds ratios for NHL were 1.2 (95% CI, 1.0–1.5) for men who had ever farmed, and 1.1 (95% CI, 0.7–1.9; 26 exposed cases; adjusted for vital status, age, state, cigarette smoking status, family history of lymphohaematopoietic cancer, high-risk occupations, and high-risk exposures) for ever handling glyphosate. [There was low power to assess the risk of NHL associated with exposure to glyphosate. There was no adjustment for other pesticides. These data were included in the pooled analysis by De Roos *et al.* (2003).]

Brown *et al.* (1993) reported the results of a study to evaluate the association between multiple myeloma and agricultural risk factors in the midwest USA (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). A population-based case–control study of 173 white men with multiple myeloma and 650 controls was conducted in Iowa, USA, an area with a large farming population. A non-significantly elevated risk of multiple myeloma was seen among farmers compared with never-farmers. The odds ratio related to exposure to glyphosate was 1.7 (95% CI, 0.8–3.6; 11 exposed cases). [This study had limited power to assess the association between multiple myeloma and exposure to glyphosate. Multiple myeloma is now considered to be a subtype of NHL.]

De Roos *et al.* (2003) used pooled data from three case–control studies of NHL conducted in the 1980s in Nebraska (Zahm *et al.*, 1990), Kansas (Hoar *et al.*, 1986), and in Iowa and Minnesota (Cantor *et al.*, 1992) (see the *Monograph* on Malathion, Section 2.0, for a detailed description of these studies) to examine pesticide exposures in farming as risk factors for NHL in men. The study population included 870 cases and 2569 controls; 650 cases and 1933 controls were included for the analysis of 47 pesticides controlling for potential confounding by other pesticides. Both logistic regression and hierarchical regression (adjusted estimates were based on prior distributions for the pesticide effects, which provides more conservative estimates than logistic regression) were used in data analysis, and all models were essentially adjusted for age, study site, and other pesticides. Reported use of glyphosate as well as several individual pesticides was associated with increased incidence of NHL. Based on 36 cases exposed, the odds ratios for the association between exposure to glyphosate and NHL were 2.1 (95% CI, 1.1–4.0) in the logistic regression analyses and 1.6 (95% CI, 0.9–2.8) in the hierarchical regression analysis. [The numbers of cases and controls were lower than those in the pooled analysis by Waddell *et al.* (2001) because only subjects with no missing data on pesticides were included. The strengths of this study when compared with other studies are that it was large,

Table 2.2 Case–control studies of leukaemia and lymphoma and exposure to glyphosate

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
USA							
Brown et al. (1990) Iowa and Minnesota, USA 1981–1983	Cases: 578 (340 living, 238 deceased) (response rate, 86%); cancer registry or hospital records Controls: 1245 (820 living, 425 deceased) (response rate, 77–79%); random-digit dialling for those aged < 65 years and Medicare for those aged ≥ 65 years Exposure assessment method: questionnaire	Leukaemia	Any glyphosate	15	0.9 (0.5–1.6)	Age, vital status, state, tobacco use, family history lymphopoietic cancer, high-risk occupations, high risk exposures	[Strengths: large population based study in a farming area. Limitations: not controlled for exposure to other pesticides. Limited power for glyphosate exposure]
Cantor et al. (1992) Iowa and Minnesota, USA 1980–1982	Cases: 622 (response rate, 89.0%); Iowa health registry records and Minnesota hospital and pathology records Controls: 1245 (response rate, 76–79%); population-based; no cancer of the lympho-haematopoietic system; frequency-matched to cases by age (5-year group), vital status, state. Random-digit dialling (aged < 65 years); Medicare records (aged ≥ 65 years); state death certificate files (deceased subjects) Exposure assessment method: questionnaire, in-person interview	NHL	Ever handled glyphosate	26	1.1 (0.7–1.9)	Age, vital status, state, smoking status, family history lymphopoietic cancer, high-risk occupations, high-risk exposures	Data subsequentially pooled in De Roos et al. (2003); white men only [Strengths: large population-based study in farming areas. Limitations: not controlled for exposure to other pesticides. Limited power for glyphosate exposure]

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Brown *et al.* (1990) Iowa, USA 1981–1984	Cases: 173 (response rate, 84%); Iowa health registry Controls: 650 (response rate, 78%); Random-digit dialling (aged < 65 years) and Medicare (aged > 65 years) Exposure assessment method: questionnaire	Multiple myeloma	Any glyphosate	11	1.7 (0.8–3.6)	Age, vital status	[Strengths: population-based study. Areas with high prevalence of farming. Limitations: limited power for glyphosate exposure]
De Roos *et al.* (2003) Nebraska, Iowa, Minnesota, Kansas, USA 1979–1986	Cases: 650 (response rate, 74.7%); cancer registries and hospital records Controls: 1933 (response rate, 75.2%); random-digit dialling, Medicare, state mortality files Exposure assessment method: questionnaire, interview (direct or next-of-kin)	NHL	Any glyphosate exposure	36	2.1 (1.1–4)	Age, study area, other pesticides	Both logistic regression and hierarchical regression were used in data analysis, the latter providing more conservative estimates [Strengths: increased power when compared with other studies, population-based, and conducted in farming areas. Advanced analytical methods to account for multiple exposures] Included participants from Cantor *et al.* (1992), Zahm *et al.* (1990), Hoar *et al.* (1986), and Brown *et al.* (1990)

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Lee et al. (2004a) Iowa, Minnesota and Nebraska, USA 1980–1986	Cases: 872 (response rate, NR); diagnosed with NHL from 1980 to 1986 Controls: 2381 (response rate, NR); frequency-matched controls Exposure assessment method: questionnaire; information on use of pesticides and history of asthma was based on interviews	NHL	Exposed to glyphosate – non-asthmatics Exposed to glyphosate – asthmatics	53 6	1.4 (0.98–2.1) 1.2 (0.4–3.3)	Age, vital status, state	177 participants (45 NHL cases, 132 controls) reported having been told by their doctor that they had asthma
Canada							
McDuffie et al. (2001) Canada 1991–1994	Cases: 517 (response rate, 67.1%), from cancer registries and hospitals Controls: 1506 (response rate, 48%); random sample from health insurance and voting records Exposure assessment method: questionnaire, some administered by telephone, some by post	NHL	Exposed to glyphosate Unexposed > 0 and ≤ 2 days > 2 days	51 464 28 23	1.2 (0.83–1.74) 1 1.0 (0.63–1.57) 2.12 (1.2–3.73)	Age, province of residence	Cross-Canada study [Strengths: large population based study. Limitations: no quantitative exposure data. Exposure assessment by questionnaire. Relatively low participation]

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Karunanayake et al. (2012) Six provinces in Canada (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia) 1991–1994	Incident cases: 316 (response rate, 68.4%); men aged ≥ 19 years; ascertained from provincial cancer registries, except in Quebec (hospital ascertainment) Controls: 1506 (response rate, 48%); matched by age ± 2 years to be comparable with the age distribution of the entire case group (HL, NHL, MM, and STS) within each province of residence. Potential controls (men aged ≥ 19 years) selected at random within age constraints from the provincial health insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario), or voters' lists (British Columbia) Exposure assessment method: questionnaire; stage 1 used a self-administered postal questionnaire; and in stage 2 detailed pesticide exposure information was collected by telephone interview	HL (ICDO2 included nodular sclerosis (M9656/3; M9663/3; M9664/3; M9665/3; M9666/3; M9667/3), lymphocytic predominance (M9651/3; M9657/3; M9658/3; M9659/3), mixed cellularity (M9652/3), lymphocytic depletion (M9653/3; M9654/3), miscellaneous (other M9650-M9669 codes for HL)	Glyphosate-based formulation	38	1.14 (0.74–1.76)	Age group, province of residence	Cross Canada study Based on the statistical analysis of pilot study data, it was decided that the most efficient definition of pesticide exposure was a cumulative exposure ≥ 10 hours/year to any combination of pesticides. This discriminated (a) between incidental, bystander, and environmental exposure vs more intensive exposure, and (b) between cases and controls [Strengths: large study. Limitations: low response rates]
			Glyphosate-based formulation	38	0.99 (0.62–1.56)	Age group, province of residence, medical history	

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Kachuri et al. (2015) Six Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario and Quebec) 1991–1994	Cases: 342 (response rate, 58%); men aged ≥ 19 years diagnosed between 1991 and 1994 were ascertained from provincial cancer registries except in Quebec, where ascertained from hospitals Controls: 1357 (response rate, 48%); men aged ≥ 19 years selected randomly using provincial health insurance records, random digit dialling, or voters' lists, frequency-matched to cases by age (±2 years) and province of residence Exposure assessment method: questionnaire	Multiple myeloma	Glyphosate use Use of glyphosate (> 0 and ≤ 2 days per year) Use of glyphosate (> 2 days per year)	32 15 12	1.19 (0.76–1.87) 0.72 (0.39–1.32) 2.04 (0.98–4.23)	Age, province of residence, use of a proxy respondent, smoking status, medical variables, family history of cancer	Cross-Canada study [Strengths: population-based case–control study. Limitations: relatively low response rates]
Sweden							
Nordström et al. (1998) Sweden 1987–1992	Cases: 111 (response rate, 91%); 121 HCL cases in men identified from Swedish cancer registry Controls: 400 (response rate, 83%); 484 (four controls/case) matched for age and county; national population registry Exposure assessment method: questionnaire, considered exposed if minimum exposure of 1 working day (8 h) and an induction period of at least 1 year	HCL	Exposed to glyphosate	4	3.1 (0.8–12)	Age	Overlaps with Hardell et al. (2002). HCL is a subtype of NHL [Strengths: population-based case–control study. Limitations: Limited power. There was no adjustment for other exposures]

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hardell & Eriksson (1999) Northern and middle Sweden 1987–1990	Cases: 404 (192 deceased) (response rate, 91%); regional cancer registries Controls: 741 (response rate, 84%); live controls matched for age and county were recruited from the national population registry, and deceased cases matched for age and year of death were identified from the national registry for causes of death Exposure assessment method: questionnaire	NHL (ICD-9 200 and 202)	Ever glyphosate – univariate Ever glyphosate – multivariate	4 NR	2.3 (0.4–13) 5.8 (0.6–54)	Not specified in the multivariable analysis	Overlaps with Hardell *et al.* (2002) [Strengths: population-based study. Limitations: few subjects were exposed to glyphosate and the study had limited power. Analyses were "multivariate" but covariates were not specified]
Hardell *et al.* (2002) Sweden; four Northern counties and three counties in mid Sweden 1987–1992	Cases: 515 (response rate, 91% in both studies); Swedish cancer registry Controls: 1141 (response rates, 84% and 83%%); national population registry Exposure assessment method: questionnaire	NHL and HCL	Ever glyphosate exposure (univariate) Ever glyphosate exposure (multivariate)	8 8	3.04 (1.08–8.5) 1.85 (0.55–6.2)	Age, county, study site, vital status, other pesticides in the multivariate analysis	Overlaps with Nordström *et al.* (1998) and Hardell & Eriksson (1999). [Strengths: large population-based study. Limitations: limited power for glyphosate exposure]

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Eriksson et al. (2008) Sweden. Four health service areas (Lund, Linkoping, Orebro and Umea) 1999–2002	Cases: 910 (response rate, 91%); incident NHL cases were enrolled from university hospitals Controls: 1016 (response rate, 92%); national population registry Exposure assessment method: questionnaire	NHL	Any glyphosate	29	2.02 (1.1–3.71)	Age, sex, year of enrolment	[Strengths: population-based case-control. Limitations: limited power for glyphosate] * Exposure to other pesticides (e.g. MPCA) controlled in the analysis
			Any glyphosate*	29	1.51 (0.77–2.94)		
			≤ 10 days per year use	12	1.69 (0.7–4.07)		
			> 10 days per year use	17	2.36 (1.04–5.37)		
		NHL	1–10 yrs	NR	1.11 (0.24–5.08)		
			> 10 yrs	NR	2.26 (1.16–4.4)		
		B-cell lymphoma	Exposure to glyphosate	NR	1.87 (0.998-3.51)		
		Lymphocytic lymphoma/B-CLL	Exposure to glyphosate	NR	3.35 (1.42–7.89)		
		Diffuse large B-cell lymphoma	Exposure to glyphosate	NR	1.22 (0.44–3.35)		
		Follicular, grade I–III	Exposure to glyphosate	NR	1.89 (0.62–5.79)		
		Other specified B-cell lymphoma	Exposure to glyphosate	NR	1.63 (0.53–4.96)		
		Unspecified B-cell lymphoma	Exposure to glyphosate	NR	1.47 (0.33-6.61)		
		T-cell lymphoma	Exposure to glyphosate	NR	2.29 (0.51–10.4)		
		Unspecified NHL	Exposure to glyphosate	NR	5.63 (1.44–22)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Other studies in Europe							
Orsi *et al.* (2009) France 2000–2004	Cases: 491 (response rate, 95.7%); cases (244 NHL; 87 HL; 104 LPSs; 56 MM) were recruited from main hospitals of the French cities of Brest, Caen, Nantes, Lille, Toulouse and Bordeaux, aged 20–75 years; ALL cases excluded Controls: 456 (response rate, 91.2%); matched on age and sex, recruited in the same hospitals as the cases, mainly in orthopaedic and rheumatological departments and residing in the hospital's catchment area Exposure assessment method: questionnaire	NHL	Any glyphosate exposure	12	1.0 (0.5–2.2)	Age, centre, socioeconomic category (blue/ white collar)	[Limitations: limited power for glyphosate]
		HL	Any exposure to glyphosate	6	1.7 (0.6–5)		
		LPS	Any exposure to glyphosate	4	0.6 (0.2–2.1)		
		MM	Any exposure to glyphosate	5	2.4 (0.8–7.3)		
		All lymphoid neoplasms	Any exposure to glyphosate	27	1.2 (0.6–2.1)		
		NHL, diffuse large cell lymphoma	Occupational use of glyphosate	5	1.0 (0.3–2.7)		
		NHL, follicular lymphoma	Occupational exposure to glyphosate	3	1.4 (0.4–5.2)		
		LPS/CLL	Occupational exposure to glyphosate	2	0.4 (0.1–1.8)		
		LPS/HCL	Occupational exposure to glyphosate	2	1.8 (0.3–9.3)		

Table 2.2 (continued)

Reference, location, enrolment period	Population size, description, exposure assessment method	Organ site (ICD code)	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cocco *et al.* (2013) Czech Republic, France, Germany, Italy, Ireland and Spain 1998–2004	Cases: 2348 (response rate, 88%); cases were all consecutive adult patients first diagnosed with lymphoma during the study period, resident in the referral area of the participating centres Controls: 2462 (response rate, 81% hospital; 52% population); controls from Germany and Italy were randomly selected by sampling from the general population and matched to cases on sex, 5-year age-group, and residence area. The rest of the centres used matched hospital controls, excluding diagnoses of cancer, infectious diseases and immunodeficiency diseases Exposure assessment method: questionnaire; support of a crop-exposure matrix to supplement the available information, industrial hygienists and occupational experts in each participating centre reviewed the general questionnaires and job modules to assess exposure to pesticides	B-cell lymphoma	Occupational exposure to glyphosate	4	3.1 (0.6–17.1)	Age, sex, education, centre	EPILYMPH case-control study in six European countries

ALL, acute lymphocytic leukaemia; B-CLL, chronic lymphocytic leukaemia; CLL, chronic lymphocytic leukaemia; HCL, hairy cell leukaemia; HL, Hodgkin lymphoma; LPS, lymphoproliferative syndrome; MCPA, 2-methyl-4-chlorophenoxyacetic acid; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NR, not reported; ref., reference; STS, soft tissue sarcoma

population-based, and conducted in farming areas. Potential confounding from multiple exposures was accounted for in the analysis.]

Using the data set of the pooled population-based case–control studies in Iowa, Minnesota, and Nebraska, USA, Lee *et al.* (2004a) investigated whether asthma acts as an effect modifier of the association between pesticide exposure and NHL. The study included 872 cases diagnosed with NHL from 1980 to 1986 and 2381 frequency-matched controls. Information on use of pesticides and history of asthma was based on interviews. A total of 177 subjects (45 cases, 132 controls) reported having been told by their doctor that they had asthma. Subjects with a history of asthma had a non-significantly lower risk of NHL than non-asthmatics, and there was no main effect of pesticide exposure. In general, asthmatics tended to have larger odds ratios associated with exposure to pesticides than non-asthmatics. There was no indication of effect modification: the odds ratio associated with glyphosate use was 1.4 (95% CI, 0.98–2.1; 53 exposed cases) among non-asthmatics and 1.2 (95% CI, 0.4–3.3; 6 exposed cases) for asthmatics, when compared with non-asthmatic non-exposed farmers). [This analysis overlapped with that of De Roos *et al.* (2003).]

(b) The cross-Canada case–control study

McDuffie *et al.* (2001) studied the associations between exposure to specific pesticides and NHL in a multicentre population-based study with 517 cases and 1506 controls among men of six Canadian provinces (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). Odds ratios of 1.26 (95% CI, 0.87–1.80; 51 exposed cases; adjusted for age and province) and 1.20 (95% CI, 0.83–1.74, adjusted for age, province, high-risk exposures) were observed for exposure to glyphosate. In an analysis by frequency of exposure to glyphosate, participants with > 2 days of exposure per year had an odds ratio of 2.12 (95% CI, 1.20–3.73, 23 exposed cases) compared with those with some, but ≤ 2 days of exposure. [The study was large, but had relatively low participation rates.]

Kachuri *et al.* (2013) investigated the association between lifetime use of pesticides and multiple myeloma in a population-based case–control study among men in six Canadian provinces between 1991 and 1994 (see the *Monograph* on Malathion, Section 2.0, for a detailed description of this study). Data from 342 cases of multiple myeloma and 1357 controls were obtained for ever-use of pesticides, number of pesticides used, and days per year of pesticide use. The odds ratios were adjusted for age, province of residence, type of respondent, smoking and medical history. The odds ratio for ever-use of glyphosate was 1.19 (95% CI, 0.76–1.87; 32 cases). When the analysis was conducted by level of exposure, no association was found for light users (≤ 2 days per year) of glyphosate (OR, 0.72; 95% CI, 0.39–1.32; 15 exposed cases) while the odds ratio in heavier users (> 2 days per year) was 2.04 (95% CI, 0.98–4.23; 12 exposed cases). [The study had relatively low response rates. Multiple myeloma is now considered a subtype of NHL.]

(c) Case–control studies in Sweden

Nordström *et al.* (1998) conducted a population case–control study in Sweden on hairy cell leukaemia (considered to be a subgroup of NHL). The study included 121 cases in men and 484 controls matched for age and sex. An age-adjusted odds ratio of 3.1 (95% CI, 0.8–12; 4 exposed cases) was observed for exposure to glyphosate. [This study had limited power to detect an effect, and there was no adjustment for other exposures.]

Hardell & Eriksson (1999) reported the results of a population-based case–control study on the incidence of NHL in men associated with pesticide exposure in four northern counties in Sweden. Exposure data was collected by questionnaire (also supplemented by telephone interviews) from 404 cases (192 deceased) and 741

controls (matched by age, sex, county, and vital status). Increased risks of NHL were found for subjects exposed to herbicides and fungicides. The odds ratio for ever-use of glyphosate was 2.3 (95% CI, 0.4–13; 4 exposed cases) in a univariate analysis, and 5.8 (95% CI, 0.6–54) in a multivariable analysis. [The exposure frequency was low for glyphosate, and the study had limited power to detect an effect. The variables included in the multivariate analysis were not specified. This study may have overlapped partially with those of Hardell *et al.* (2002).]

Hardell *et al.* (2002) conducted a pooled analysis of two case–control studies, one on NHL (already reported in Hardell & Eriksson, 1999) and another on hairy cell leukaemia, a subtype of NHL (already reported by Nordström *et al.*, 1998). The pooled analysis of NHL and hairy cell leukaemia was based on 515 cases and 1141 controls. Increased risk was found for exposure to glyphosate (OR, 3.04; 95% CI, 1.08–8.52; 8 exposed cases) in the univariate analysis, but the odds ratio decreased to 1.85 (95% CI, 0.55–6.20) when study, study area, and vital status were considered in a multivariate analysis. [The exposure frequency was low for glyphosate and the study had limited power. This study partially overlapped with those of Hardell & Eriksson (1999) and Nordström *et al.* (1998).]

Eriksson *et al.* (2008) reported the results of a population based case–control study of exposure to pesticides as a risk factor for NHL. Men and women aged 18–74 years living in Sweden were included from 1 December 1999 to 30 April 2002. Incident cases of NHL were enrolled from university hospitals in Lund, Linköping, Örebro, and Umeå. Controls (matched by age and sex) were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total, 910 (91%) cases and 1016 (92%) controls participated. Multivariable models included agents with statistically significant increased odds ratios (MCPA, 2-methyl-4-chlorophenoxyacetic acid), or with an odds ratio of > 1.50 and at least 10 exposed subjects (2,4,5-T and/or 2,4-D; mercurial seed dressing, arsenic, creosote, tar), age, sex, year of diagnosis or enrolment. The odds ratio for exposure to glyphosate was 2.02 (95% CI, 1.10–3.71) in a univariate analysis, and 1.51 (95% CI, 0.77–2.94) in a multivariable analysis. When exposure for more than 10 days per year was considered, the odds ratio was 2.36 (95% CI, 1.04–5.37). With a latency period of > 10 years, the odds ratio was 2.26 (95% CI, 1.16–4.40). The associations with exposure to glyphosate were reported also for lymphoma subtypes, and elevated odds ratios were reported for most of the cancer forms, including B-cell lymphoma (OR, 1.87; 95% CI, 0.998–3.51) and the subcategory of small lymphocytic lymphoma/chronic lymphocytic leukaemia (OR, 3.35; 95% CI, 1.42–7.89; [not adjusted for other pesticides]). [This was a large study; there was possible confounding from use of other pesticides including MCPA, but this was considered in the analysis.]

(d) Other case–control studies in Europe

Orsi *et al.* (2009) reported the results of a hospital-based case–control study conducted in six centres in France between 2000 and 2004. Incident cases with a diagnosis of lymphoid neoplasm aged 20–75 years and controls of the same age and sex as the cases were recruited in the same hospital, mainly in the orthopaedic and rheumatological departments during the same period. [The Working Group noted that the age of case eligibility was given in the publication as 20–75 years in the materials and methods section, but as 18–75 years in the abstract.] Exposures to pesticides were evaluated through specific interviews and case-by-case expert reviews. The analyses included 491 cases (244 cases of NHL, 87 cases of Hodgkin lymphoma), 104 of lymphoproliferative syndrome, and 56 cases of multiple myeloma), and 456 age- and sex-matched controls. Positive associations between some subtypes and occupational exposure to several pesticides

were noted. The odds ratios associated with any exposure to glyphosate were 1.2 (95% CI, 0.6–2.1; 27 exposed cases) for all lymphoid neoplasms combined, 1.0 (95% CI, 0.5–2.2; 12 exposed cases) for NHL, 0.6 (95% CI, 0.2–2.1; 4 exposed cases) for lymphoproliferative syndrome, 2.4 (95% CI, 0.8–7.3) for multiple myeloma, and 1.7 (95% CI, 0.6–5.0; 6 exposed cases) for Hodgkin lymphoma, after adjusting for age, centre, and socioeconomic category ("blue/white collar").

Cocco *et al.* (2013) reported the results of a pooled analysis of case–control studies conducted in six European countries in 1998–2004 (EPILYMPH, Czech Republic, France, Germany, Ireland, Italy, and Spain) to investigate the role of occupational exposure to specific groups of chemicals in the etiology of lymphoma overall, B-cell lymphoma, and its most prevalent subtypes. A total of 2348 incident cases of lymphoma and 2462 controls were recruited. Controls from Germany and Italy were randomly selected by sampling from the general population, while the rest of the centres used matched hospital controls. Overall, the participation rate was 88% for cases, 81% for hospital controls, and 52% for population controls. An occupational history was collected with farm work-specific questions on type of crop, farm size, pests being treated, type and schedule of pesticide use. In each study centre, industrial hygienists and occupational experts assessed exposure to specific groups of pesticides and individual compounds with the aid of agronomists. [Therefore any exposure misclassification would be non-differential.] Analyses were conducted for lymphoma and the most prevalent lymphoma subtypes adjusting for age, sex, education, and centre. Lymphoma overall, and B-cell lymphoma were not associated with any class of the investigated pesticides, while the risk of chronic lymphocytic leukaemia was elevated among those ever exposed to inorganic and organic pesticides. Only for a few individual agrochemicals was there a sizeable number of study subjects to conduct a meaningful analysis, and the odds ratio for exposure to glyphosate and B-cell lymphoma was 3.1 (95% CI, 0.6–17.1; 4 exposed cases and 2 exposed controls). [The study had a very limited power to assess the effects of glyphosate on risk of NHL.]

2.2.2 Other haematopoietic cancers

Orsi *et al.* (2009) also reported results for Hodgkin lymphoma (see Section 2.2.1).

Karunanayake *et al.* (2012) conducted a case–control study of Hodgkin lymphoma among white men, aged 19 years or older, in six regions of Canada (see the Malathion *Monograph*, Section 2.0, for a detailed description of this study). The analysis included 316 cases and 1506 age-matched (± 2 years) controls. Based on 38 cases exposed to glyphosate, the odds ratios were 1.14 (95% CI, 0.74–1.76) adjusted for age and province, and 0.99 (95% CI, 0.62–1.56) when additionally adjusted for medical history variables.

Brown *et al.* (1990) evaluated exposure to carcinogens in an agricultural setting and the relationship with leukaemia in a population-based case–control interview study in Iowa and Minnesota, USA, including 578 white men with leukaemia and 1245 controls. The exposure assessment was done with a personal interview of the living subjects or the next-of-kin. Farmers had a higher risk of all leukaemias compared with non-farmers, and associations were found for exposure to specific animal insecticides, including the organophosphates crotoxyphos, dichlorvos, famphur, pyrethrins, and methoxychlor. The odds ratio for glyphosate was 0.9 (95% CI, 0.5–1.6; 15 exposed cases; adjusted for vital status, age, state, tobacco use, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures). [This was a large study in an agricultural setting, but had limited power for studying the effects of glyphosate use.]

2.3 Case–control studies on other cancer sites

2.3.1 Cancer of the oesophagus and stomach

Lee *et al.* (2004b) evaluated the risk of adenocarcinomas of the oesophagus and stomach associated with farming and agricultural pesticide use. The population-based case–control study was conducted in eastern Nebraska, USA. Subjects of both sexes diagnosed with adenocarcinoma of the stomach (n = 170) or oesophagus (n = 137) between 1988 and 1993 were enrolled. Controls (n = 502) were randomly selected from the population registry of the same geographical area. The response rates were 79% for cancer of the stomach, 88% for cancer of the oesophagus, and 83% for controls. Adjusted odds ratios were estimated for use of individual and chemical classes of insecticides and herbicides, with non-farmers as the reference category. No association was found with farming or ever-use of insecticides or herbicides, or with individual pesticides. For ever-use of glyphosate, the odds ratio was 0.8 (95% CI, 0.4–1.4; 12 exposed cases) for cancer of the stomach, and 0.7 (95% CI, 0.3–1.4; 12 exposed cases) for oesophageal cancer. [The study was conducted in a farming area, but the power to detect an effect of glyphosate use was limited.]

2.3.2 Cancer of the brain

Ruder *et al.* (2004) conducted a case–control study on glioma among nonmetropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin in the Upper Midwest Health Study, USA. The study included 457 cases of glioma and 648 population-based controls, all adult men. Exposure assessment was done with interviews of the subject or the relatives. The response rates were 93% and 70% for cases and controls, respectively. No association were found with any of the pesticides assessed, including glyphosate. [Glyphosate use was assessed, but specific results were not presented.]

Carreón *et al.* (2005) evaluated the effects of rural exposures to pesticides on risk of glioma among women aged 18–80 years who were nonmetropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin in the Upper Midwest Health Study, USA. A total of 341 cases of glioma and 528 controls were enrolled. A personal interview was carried out for exposure assessment. The response rates were 90% and 72%, respectively. After adjusting for age, age group, education, and farm residence, no association with glioma was observed for exposure to several pesticide classes or individual pesticides. There was a reduced risk for glyphosate (OR, 0.7; 95% CI, 0.4–1.3; 18 exposed cases). These results were not affected by the exclusion of proxy respondents (43% of cases, 2% of controls).

Lee *et al.* (2005) evaluated the association between farming and agricultural pesticide use and risk of adult glioma in a population-based case–control study in eastern Nebraska, USA. Cases of glioma were in men and women (n = 251) and were compared with population controls from a previous study (n = 498). A telephone interview was conducted for 89% of the cases and 83% of the controls. Adjusted odds ratios for farming and for use of individual and chemical classes of insecticides and herbicides were calculated using non-farmers as the reference category. Among men, ever living or working on a farm and duration of farming were associated with significantly increased risks of glioma, but the positive findings were limited to proxy respondents. Among women, there were no positive associations with farming activities among self or proxy respondents. Some specific pesticide families and individual pesticides were associated with significantly increased risks among male farmers, but most of the positive associations were limited to proxy respondents. There was a non-significant excess risk with glyphosate use for the overall group (OR, 1.5; 95% CI, 0.7–3.1; 17 exposed cases), but there was inconsistency between observations for self-respondents (OR,

0.4; 95% CI, 0.1–1.6) and observations for proxy respondents (OR, 3.1; 95% CI, 1.2–8.2). [The study had limited power to detect an effect of glyphosate use, and the inconsistencies for self and proxy respondents made the results difficult to interpret.]

2.3.3 Soft tissue sarcoma

Pahwa *et al.* (2011) reported the results of the soft tissue sarcoma component of the cross-Canada study in relation to specific pesticides, including 357 cases of soft tissue sarcoma and 1506 population controls from 1991–1994. The fully adjusted odds ratio for glyphosate use was 0.90 (95% CI, 0.58–1.40).

2.3.4 Cancer of the prostate

Band *et al.* (2011) report results of a case–control study including 1516 patients with cancer of the prostate (ascertained by the cancer registry of British Columbia, Canada, for 1983–90) and 4994 age-matched controls with cancers at all other cancer sites excluding lung and unknown primary site. Agricultural exposures were assessed by job-exposure matrix. A total of 60 cases were exposed to glyphosate (adjusted OR, 1.36; 95% CI, 0.83–2.25).

2.3.5 Childhood cancer

Parental exposure to pesticides, including glyphosate, was assessed in a population-based case–control study of childhood leukaemia in Costa Rica (Monge *et al.*, 2007). However, associations of childhood cancer with glyphosate were reported only for an "other pesticides" category that also included paraquat, chlorothalonil, and other chemicals. [Because glyphosate was not specifically assessed, this study was not evaluated by the Working Group.]

2.4. Meta-analyses

Schinasi & Leon (2014) conducted a systematic review and meta-analysis of NHL and occupational exposure to agricultural pesticides, including glyphosate. The meta-analysis for glyphosate included six studies (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; De Roos *et al.*, 2003; 2005a; Eriksson *et al.*, 2008; Orsi *et al.*, 2009) and yielded a meta risk-ratio of 1.5 (95% CI, 1.1–2.0). [The Working Group noted that the most fully adjusted risk estimates from the articles by Hardell *et al.* (2002) and Eriksson *et al.* (2008) were not used in this analysis. After considering the adjusted estimates of the two Swedish studies in the meta-analysis, the Working Group estimated a meta risk-ratio of 1.3 (95% CI, 1.03–1.65), I^2 = 0%, *P* for heterogeneity 0.589.]

3. Cancer in Experimental Animals

3.1 Mouse

See Table 3.1

3.1.1 Dietary administration

Groups of 50 male and 50 female CD-1 mice [age not reported] were given diets containing glyphosate (purity, 99.7%) at a concentration of 0, 1000, 5000, or 30 000 ppm, ad libitum, for 24 months. There was no treatment-related effect on body weight in male and female mice at the lowest or intermediate dose. There was a consistent decrease in body weight in the male and female mice at the highest dose compared with controls. Survival in all dose groups was similar to that of controls. There was a positive trend (*P* = 0.016, trend test; see EPA, 1985b) in the incidence of renal tubule adenoma in dosed male mice: 0/49, 0/49, 1/50 (2%), 3/50 (6%). [The Working Group noted that renal tubule adenoma is a rare tumour in CD-1 mice.] No data on tumours of the kidney

Table 3.1 Studies of carcinogenicity with glyphosate in mice

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, CD-1 (M, F) 24 mo EPA (1985a, b, 1986, 1991a)	Diet containing glyphosate (technical grade; purity, 99.7%) at concentrations of 0, 1000, 5000, or 30 000 ppm, ad libitum, for 24 mo 50 M and 50 F/group [age, NR]	*Males* Renal tubule adenoma: 0/49, 0/49, 1/50 (2%), 3/50 (6%) *Females* No data provided on the kidney Report from the PWG of the EPA (1986): *Males* Renal tubule adenoma: 1/49 (2%), 0/49, 0/50, 1/50 (2%) Renal tubule carcinoma: 0/49, 0/49, 1/50 (2%), 2/50 (4%) Renal tubule adenoma or carcinoma (combined): 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%)	*P* for trend = 0.016; see Comments [NS] [*P* = 0.037; Cochran–Armitage trend test] [*P* = 0.034; Cochran–Armitage trend test]	No information was provided on renal tubule adenomas in female mice, or on statistical analyses of tumour data EPA recommended that additional renal sections be cut and evaluated from all control and treated male mice. The pathology report for these additional sections (EPA, 1985b) showed the same incidence of renal tubule adenomas as originally reported, with no significant difference in incidence when comparing control and treated groups; however, the test for linear trend in proportions resulted in *P* = 0.016 EPA (1986) convened a PWG and requested additional pathological and statistical information on kidney tumours observed in male mice treated with glyphosate
Mouse, CD-1 (M, F) 104 wk JMPR (2009)	Diet containing glyphosate (purity, 98.6%) at doses of 0, 100, 300, 1000 mg/kg bw, ad libitum, for 104 wk 50 M and 50 F/group [age, NR]	*Males* Haemangiosarcoma: 0/50, 0/50, 0/50, 4/50 (8%) Histiocytic sarcoma in the lymphoreticular/haemopoietic tissue: 0/50, 2/50 (4%), 0/50, 2/50 (4%) *Females* Haemangiosarcoma: 0/50, 2/50 (4%), 0/50, 1/50 (2%) Histiocytic sarcoma in the lymphoreticular/haemopoietic tissue: 0/50, 3/50 (6%), 3/50 (6%), 1/50 (2%)	[*P* < 0.001; Cochran–Armitage trend test] NS NS NS	

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, Swiss (M) 32 wk George *et al.* (2010)	Initiation–promotion study Skin application of glyphosate-based formulation (glyphosate, 41%; POEA, ~15%) (referred to as "glyphosate") dissolved in 50% ethanol; DMBA dissolved in 50% ethanol, and TPA dissolved in 50% acetone, used in the groups described below 20 M/group	Skin tumours [called "papillomas" by the authors, following gross examination only]		Short duration of treatment, no solvent controls, and lack of any histopathological evaluation Age at start, NR (mice weighed 12–15 g bw) [The Working Group concluded this was an inadequate study for the evaluation of glyphosate]
	Group I: untreated control (no treatment)	Group I: 0/20		
	Group II: glyphosate only: 25 mg/kg bw topically, 3 × /wk, for 32 wk	Group II: 0/20		
	Group III: single topical application of DMBA, 52 µg/mouse, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group III: 20/20*, 7.8 ± 1.1	*$P < 0.05$ vs groups VI and VII	
	Group IV: single topical application of glyphosate, 25 mg/kg bw, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group I: 0/20		
	Group V: 3 × /wk topical application of glyphosate, 25 mg/kg bw, for 3 wk, followed 1 wk later by TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group V: 0/20		
	Group VI: single topical application of DMBA, 52 µg/mouse	Group VI: 0/20		
	Group VII: topical application of TPA, 5 µg/mouse, 3 × /wk, for 32 wk	Group VII: 0/20		
	Group VIII: single topical application of DMBA, 52 µg/mouse, followed 1 wk later by topical treatment with glyphosate, 25 mg/kg bw, 3 × /wk, for 32 wk	Group VIII: 8/20*, 2.8 ± 0.9	*$P < 0.05$ vs group VI	

bw, body weight; DMBA, 7,12-dimethylbenz[*a*]anthracene; EPA, United States Environmental Protection Agency; F, female; M, male; mo, month; NR, not reported; NS, not significant; POEA, polyethoxylated tallowamine; PWG, pathology working group; TPA, 12-*O*-tetradecanoyl-phorbol-13-acetate; vs, versus; wk, week; yr, year

were provided for female mice. No other tumour sites were identified (EPA, 1985a). Subsequent to its initial report (EPA, 1985a), the United States Environmental Protection Agency (EPA) recommended that additional renal sections be cut and evaluated from all male mice in the control and treated groups. The pathology report for these additional sections (EPA, 1985b) indicated the same incidence of renal tubule adenoma as originally reported, with no significant increase in incidence between the control group and treated groups by pairwise comparison. However, as already reported above, the test for linear trend in proportions resulted in a significance of $P = 0.016$. The EPA (1986) also requested that a pathology working group (PWG) be convened to evaluate the tumours of the kidney observed in male mice treated with glyphosate, including the additional renal sections. In this second evaluation, the PWG reported that the incidence of adenoma of the renal tubule was 1/49 (2%), 0/49, 0/50, 1/50 (2%) [not statistically significant]; the incidence of carcinoma of the renal tubule was 0/49, 0/49, 1/50 (2%), 2/50 (4%) [$P = 0.037$, trend test for carcinoma]; and the incidence of adenoma or carcinoma (combined) of the renal tubule was 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%) [$P = 0.034$, trend test for combined]. [The Working Group considered that this second evaluation indicated a significant increase in the incidence of rare tumours, with a dose-related trend, which could be attributed to glyphosate. Chandra & Frith (1994) reported that only 1 out of 725 [0.14%] CD-1 male mice in their historical database had developed renal cell tumours (one carcinoma).]

[The Working Group noted the differences in histopathological diagnosis between pathologists. Proliferative lesions of the renal tubules are typically categorized according to published criteria as hyperplasia, adenoma, or carcinoma. The difference is not trivial, because focal hyperplasia, a potentially preneoplastic lesion, should be carefully differentiated from the regenerative changes of the tubular epithelium. There is a morphological continuum in the development and progression of renal neoplasia. Thus larger masses may exhibit greater heterogeneity in histological growth pattern, and cytologically more pleomorphism and atypia than smaller lesions (Eustis *et al.*, 1994). Of note, a renal tumour confirmed by the PWG after re-evaluation of the original slides (EPA, 1986), had not been seen in the re-sectioned kidney slides (EPA, 1985b). This may be related to the growth of tumour that – in contrast to tumours in other organs – is not spherical but elliptical because of the potential expansion in tubules. In addition, the concept of tubular expansion without compression of adjacent parenchyma may be at the basis of the discrepancy between the first (EPA, 1985a, b) and second evaluation (EPA, 1986).]

In another study reported to the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), groups of 50 male and 50 female CD-1 mice [age at start not reported] were given diets containing glyphosate (purity, 98.6%) at a concentration that was adjusted weekly for the first 13 weeks and every 4 weeks thereafter to give doses of 0, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 weeks (JMPR, 2006). There was no treatment-related effect on body weight or survival in any of the dosed groups. There was an increase in the incidence of haemangiosarcoma in males – 0/50, 0/50, 0/50, 4/50 (8%) [$P < 0.001$, Cochran–Armitage trend test], and in females – 0/50, 2/50 (4%), 0/50, 1/50 (2%) [not statistically significant], and an increase in the incidence of histiocytic sarcoma in the lymphoreticular/haemopoietic tissue in males – 0/50, 2/50 (4%), 0/50, 2/50 (4%), and in females – 0/50, 3/50 (6%), 3/50 (6%), 1/50 (2%) [not statistically significant for males or females]. [The Working Group considered that this study was adequately reported.]

3.1.2 Initiation–promotion

Groups of 20 male Swiss mice [age at start not reported; body weight, 12–15 g] were given a glyphosate-based formulation (glyphosate, 41%; polyethoxylated tallowamine, ~15%) (referred to as glyphosate in the article) that was dissolved in 50% ethanol and applied onto the shaved back skin (George *et al.*, 2010). Treatment groups were identified as follows:

- Group I – untreated control;
- Group II – glyphosate only (25 mg/kg bw), applied topically three times per week for 32 weeks;
- Group III – single topical application of dimethylbenz[*a*]anthracene (DMBA; in ethanol; 52 µg/mouse), followed 1 week later by 12-*O*-tetradecanoylphorbol-13-acetate (TPA; in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks;
- Group IV – single topical application of glyphosate (25 mg/kg bw) followed 1 week later by TPA (in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks;
- Group V – glyphosate (25 mg/kg bw) applied topically three times per week for 3 weeks (total of nine applications), followed 1 week later by TPA (in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks;
- Group VI – single topical application of DMBA (in ethanol; 52 µg/mouse);
- Group VII –TPA (in acetone; 5 µg/mouse), applied topically three times per week for 32 weeks; and
- Group VIII –single topical application of DMBA (in ethanol; 52 µg/mouse), followed 1 week later by glyphosate (25 mg/kg bw), applied topically three times per week for 32 weeks.

All mice were killed at 32 weeks. Skin tumours were observed only in group III (positive control, DMBA + TPA, 20/20) and group VIII (DMBA + glyphosate, 8/20; $P < 0.05$ versus group VI [DMBA only, 0/20]). No microscopic examination was conducted and tumours were observed "as a minute wart like growth [that the authors called squamous cell papillomas], which progressed during the course of experiment." [The glyphosate formulation tested appeared to be a tumour promoter in this study. The design of the study was poor, with short duration of treatment, no solvent controls, small number of animals, and lack of histopathological examination. The Working Group concluded that this was an inadequate study for the evaluation of glyphosate.]

3.1.3 Review articles

Greim *et al.* (2015) have published a review article containing information on five long-term bioassay feeding studies in mice. Of these studies, one had been submitted for review to the EPA (EPA, 1985a, b, 1986, 1991a), and one to the JMPR (JMPR, 2006); these studies are discussed in Section 3.1.1. The review article reported on an additional three long-term bioassay studies in mice that had not been previously available in the open literature, but had been submitted to various organizations for registration purposes. The review article provided a brief summary of each study and referred to an online data supplement containing the original data on tumour incidence from study reports. The three additional long-term bioassay studies in mice are summarized below. [The Working Group was unable to evaluate these studies, which are not included in Table 3.1 and Section 5.3, because the information provided in the review article and its supplement was insufficient (e.g. information was lacking on statistical methods, choice of doses, body-weight gain, survival data, details of histopathological examination, and/or stability of dosed feed mixture).]

In the first study (identified as Study 12, 1997a), groups of 50 male and 50 female CD-1

mice [age at start not reported] were given diets containing glyphosate (purity, 94–96%) at a concentration of 0, 1600, 8000, or 40 000 ppm for 18 months. The increase in the incidence of bronchiolo-alveolar adenoma and carcinoma, and of lymphoma, was reported to be not statistically significant in males and females receiving glyphosate. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In the second study (identified as Study 13, 2001), groups of 50 male and 50 female Swiss albino mice [age at start not reported] were given diets containing glyphosate (purity, > 95%) at a concentration of 0 (control), 100, 1000, or 10 000 ppm for 18 months. The authors reported a statistically significant increase in the incidence of malignant lymphoma (not otherwise specified, NOS) in males at the highest dose: 10/50 (20%), 15/50 (30%), 16/50 (32%), 19/50 (38%; $P < 0.05$; pairwise test); and in females at the highest dose: 18/50 (36%), 20/50 (40%), 19/50 (38%), 25/50 (50%; $P < 0.05$; pairwise test). [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In the third study (identified as Study 14, 2009a), groups of 51 male and 51 female CD-1 mice [age at start not reported] were given diets containing glyphosate (purity, 94.6–97.6%) at a concentration of 0, 500, 1500, or 5000 ppm for 18 months. Incidences for bronchiolo-alveolar adenoma and carcinoma, malignant lymphoma (NOS), and hepatocellular adenoma and carcinoma in males, and for bronchiolo-alveolar adenoma and carcinoma, malignant lymphoma (NOS) and pituitary adenoma in females, were included in the article. In males, the authors reported that there was a significant positive trend [statistical test not specified] in the incidence of bronchiolo-alveolar carcinoma (5/51, 5/51, 7/51, 11/51) and of malignant lymphoma (0/51, 1/51, 2/51, 5/51). [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

3.2 Rat

See Table 3.2

3.2.1 Drinking-water

Groups of 10 male and 10 female Sprague-Dawley rats (age, 5 weeks) were given drinking-water containing a glyphosate-based formulation at a dose of 0 (control), 1.1×10^{-8}% (50×10^{-5} mg/L), 0.09% (400 mg/L) or 0.5% (2.25×10^{3} mg/L), ad libitum, for 24 months (Séralini *et al.*, 2014). [The study reported is a life-long toxicology study on a glyphosate-based formulation and on genetically modified NK603 maize, which the authors stated was designed as a full study of long-term toxicity and not a study of carcinogenicity. No information was provided on the identity or concentration of other chemicals contained in this formulation.] Survival was similar in treated and control rats. [No data on body weight were provided.] In female rats, there was an almost twofold increase in the incidence of tumours of the mammary gland (mainly fibroadenoma and adenocarcinoma) in animals exposed to the glyphosate-based formulation only versus control animals: control, 5/10 (50%); lowest dose, 9/10 (90%); intermediate dose, 10/10 (100%) [$P < 0.05$; Fisher exact test]; highest dose, 9/10 (90%). [The Working Group concluded that this study conducted on a glyphosate-based formulation was inadequate for evaluation because the number of animals per group was small, the histopathological description of tumours was poor, and incidences of tumours for individual animals were not provided.]

In another study with drinking-water, Chruscielska *et al.* (2000) gave groups of 55 male and 55 female Wistar rats (age, 6–7 weeks) drinking-water containing an ammonium salt

of glyphosate as a 13.85% solution [purity of glyphosate, not reported] that was used to make aqueous solutions of 0 (control), 300, 900, and 2700 mg/L, for 24 months [details on the dosing regimen were not reported]. The authors reported that survival and body-weight gain were similar in treated and control animals. No significant increase in tumour incidence was reported in any of the treated groups. [The Working Group noted the limited information provided on dosing regimen, histopathological examination method, and tumour incidences.]

3.2.2 Dietary administration

The JMPR report included information on a 1-year feeding study in which groups of 24 male and 24 female Wistar-Alpk:APfSD rats [age at start not reported] were given diets containing glyphosate (purity, 95.6%) at a concentration of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 1 year (JMPR, 2006). There was a treatment-related decrease in body-weight gain at the two highest doses (significant at 20 000 ppm for both sexes, and at 8000 ppm only in females). There was no treatment-related decrease in survival. No significant increase in tumour incidence was observed in any of the treated groups. [The Working Group noted the short duration of exposure.]

The JMPR report also included information on a 104-week feeding study in which groups of 50 male and 50 female Sprague-Dawley rats [age at start not reported] were given diets containing glyphosate (purity, 98.7–98.9%) at a concentration that was adjusted to provide doses of 0, 10, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 weeks (JMPR, 2006). There was a treatment-related decrease in body-weight gain in males and females at the highest dose. There was no significant treatment-related decrease in survival or increase in tumour incidence in any of the treated groups.

Information was also included in the JMPR report on a 24-month feeding study in which groups of 52 male and 52 female Wistar-Alpk:APfSD rats [age at start not reported] were given diets containing glyphosate (purity, 97.6%) at a concentration of 0, 2000, 6000, or 20 000 ppm, ad libitum, for 24 months (JMPR, 2006). There was a treatment-related decrease in body-weight gain in males and females at the highest dose, and a corresponding significant increase in survival in males. No significant increase in tumour incidence was observed in any of the treated groups.

The EPA (1991a, b, c, d) provided information on a long-term study in which groups of 60 male and 60 female Sprague-Dawley rats (age, 8 weeks) were given diets containing glyphosate (technical grade; purity, 96.5%) at a concentration of 0 ppm, 2000 ppm, 8000 ppm, or 20 000 ppm, ad libitum, for 24 months. Ten animals per group were killed after 12 months. There was no compound-related effect on survival, and no statistically significant decreases in body-weight gain in male rats. In females at the highest dose, body-weight gain was significantly decreased, starting on day 51. In males at the lowest dose, there was a statistically significant increase in the incidence of pancreatic islet cell adenoma compared with controls: 8/57 (14%) versus 1/58 (2%), $P \leq 0.05$ (Fisher exact test). Additional analyses by the EPA (1991a) (using the Cochran–Armitage trend test and Fisher exact test, and excluding rats that died or were killed before week 55) revealed a statistically significant higher incidence of pancreatic islet cell adenoma in males at the lowest and highest doses compared with controls: lowest dose, 8/45 (18%; $P = 0.018$; pairwise test); intermediate dose, 5/49 (10%); highest dose, 7/48 (15%; $P = 0.042$; pairwise test) versus controls, 1/43 (2%). The range for historical controls for pancreatic islet cell adenoma reported in males at this laboratory was 1.8–8.5%. [The Working Group noted that there was no statistically significant positive trend in the incidence of these tumours, and no apparent progression to carcinoma.] There was also a statistically significant positive trend in the incidence of hepatocellular adenoma in

Table 3.2 Studies of carcinogenicity with glyphosate in rats

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) 24 mo Séralini *et al.* (2014)	Drinking-water containing a glyphosate-based formulation at a concentration of 0 (control), 1.1×10^{-8}% (glyphosate, 5.0×10^{-5} mg/L), 0.09% (glyphosate, 400 mg/L) or 0.5% (glyphosate, 2.25×10^{3} mg/L), ad libitum, for 24 mo 10 M and 10 F/group (age, 5 wk)	*Males* No significant increase in tumour incidence observed in any of the treated groups *Females* Mammary tumours (mainly fibroadenomas and adenocarcinomas): 5/10 (50%), 9/10 (90%), 10/10 (100%)*, 9/10 (90%) Pituitary lesions (hypertrophy, hyperplasia, and adenoma): 6/10 (60%), 8/10 (80%), 7/10 (70%), 7/10 (70%)	NS *[$P < 0.05$] [NS]	Data are from an in-depth life-long toxicology study on a glyphosate-based formulation and NK603 genetically modified maize; authors stated that the study was designed as a full chronic toxicity and not a carcinogenicity study. No information provided on the identity or concentration of other chemicals contained in this formulation Histopathology poorly described and tumour incidences for individual animals not discussed in detail. Small number of animals per group [The Working Group concluded this was an inadequate study for the evaluation of glyphosate carcinogenicity]
Rat, Wistar (M, F) 24 mo Chruscielska *et al.* (2000)	Drinking-water containing ammonium salt of glyphosate (13.85% solution) [purity of glyphosate, NR] was used to make aqueous solutions of 0, 300, 900, and 2700 mg/L [Details on dosing regimen, NR] 55 M and 55 F/group (age, 6–7 wk)	No significant increase in tumour incidence observed in any of the treated groups	NS	Limited information on dosing regimen, histopathological examination methods, and tumour incidences
Rat, Wistar-Alpk:APfSD (M, F) 1 yr JMPR (2006)	Diet containing glyphosate (purity, 95.6%) at concentrations of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 1 yr 24 M and 24 F/group [age, NR]	No significant increase in tumour incidence observed in any groups of treated animals	NS	Short duration of exposure
Rat, Sprague-Dawley (M, F) 104 wk JMPR (2006)	Diet containing glyphosate (purity, 98.7–98.9%) at doses of 0, 10, 100, 300, or 1000 mg/kg bw, ad libitum, for 104 wk 50 M and 50 F/group [age, NR]	No significant increase in tumour incidence observed in any groups of treated animals	NS	
Rat, Wistar-Alpk:APfSD (M, F) 24 mo JMPR (2006)	Diet containing glyphosate (purity, 97.6%) at concentrations of 0, 2000, 6000, or 20 000 ppm, ad libitum, for 2 yr 52 M and 52 F/group [age, NR]	No significant increase in tumour incidence observed in any groups of treated animals	NS	

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat Sprague-Dawley (M, F) 24 mo EPA (2015a, b, c, d)	Diet containing glyphosate (technical grade; purity, 96.5%) at concentrations of 0, 2000, 8000, or 20 000 ppm, ad libitum, for 24 mo 60 M and 60 F/group (age, 8 wk) 10 rats/group killed after 12 mo	*Males* *Pancreas (islet cell):* Adenoma: 1/58 (2%), 8/57 (14%)*; 5/60 (8%), 7/59 (12%) Carcinoma: 1/58 (2%), 0/57, 0/60, 0/59 Adenoma or carcinoma (combined): 2/58 (3%), 8/57 (14%), 5/60 (8%), 7/59 (12%) *Liver:* Hepatocellular adenoma: 2/60 (3%), 2/60 (3%), 3/60 (6%), 7/60 (12%) Hepatocellular carcinoma: 3/60 (5%), 2/60 (3%), 1/60 (2%), 2/60 (3%) *Females* *Pancreas (islet cell):* Adenoma: 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 Carcinoma: 0/60, 0/60, 0/60, 0/59 Adenoma or carcinoma (combined): 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59 *Thyroid:* C-cell adenoma: 2/60 (3%), 2/60 (3%), 6/60 (10%), 6/60 (10%) C-cell carcinoma: 0/60, 0/60, 1/60, 0/60	Adenoma, * $P \leq 0.05$ (Fisher exact test with Bonferroni inequality); see comments Adenoma, P for trend = 0.016; see comments NS Adenoma, P for trend = 0.031; see comments	Historical control range for pancreatic islet cell adenoma reported in males at this laboratory, 1.8–8.5% EPA (2015a), performed additional analyses using the Cochran–Armitage trend test and Fisher exact test, and excluding animals that died or were killed before wk 54–55: *Males* *Pancreas (islet cell):* Adenoma: 1/43 (2%), 8/45 (18%; $P = 0.018$), 5/49 (10%), 7/48 (15%; $P = 0.042$) Carcinoma: 1/43 (2%), 0/45 (0%), 0/49 (0%), 0/48 (0%) Adenoma or carcinoma (combined): 2/43 (5%), 8/45 (18%), 5/49 (10%), 7/48 (15%) [There was no statistically significant positive trend in the incidence of pancreatic tumours, and no apparent progression to carcinoma] *Liver:* Hepatocellular adenoma: 2/44 (5%; P for trend = 0.016), 2/45 (4%), 3/49 (6%), 7/48 (15%) Hepatocellular carcinoma: 3/44 (7%); 2/45 (4%), 1/49 (2%), 2/48 (4%) Hepatocellular adenoma or carcinoma (combined): 5/44 (11%), 4/45 (9%), 4/49 (8%), 9/48 (19%) [There was no apparent progression to carcinoma] *Females* *Thyroid:* C-cell adenoma: 2/57 (4%; P for trend = 0.031), 2/60 (3%), 6/59 (10%), 6/55 (11%) C-cell carcinoma: 0/57, 0/60, 1/59 (2%), 0/55 C-cell adenoma or carcinoma (combined): 2/57 (4%), 2/60 (3%), 7/59 (12%), 6/55 (11%) [There was no apparent progression to carcinoma]

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat Sprague-Dawley (M, F) Lifetime (up to 26 mo) EPA (1991a, b, c, d)	Diet containing glyphosate (purity, 98.7%) at concentrations of 0 ppm, 30 ppm (3 mg/kg bw per day), 100 ppm (10 mg/kg bw per day), 300 ppm (31 mg/kg bw per day), ad libitum, up to 26 mo 50 M and 50 F/group [age, NR]	*Males* *Pancreas (islet cell):* Adenoma: 0/50 (0%), 5/49* (10%), 2/50 (4%), 2/50 (4%) Carcinoma: 0/50 (0%), 0/49 (0%), 0/50 (0%), 1/50 (2%) Adenoma or carcinoma (combined): 0/50 (0%), 5/49 (10%), 2/50 (4%), 3/50 (6%) *Females* *Pancreas (islet cell):* Adenoma: 2/50 (4%), 1/50 (2%), 1/50 (2%), 0/50 (0%) Carcinoma: 0/50 (0%), 1/50 (2%), 1/50 (2%), 1/50 (2%) Adenoma or carcinoma (combined): 2/50 (10%), 2/50 (2%), 2/50 (74%), 1/50 (2%)	Adenoma, *[$P < 0.05$; Fisher exact test] NS	[There was no statistically significant positive trend in the incidence of pancreatic tumours, and no apparent progression to carcinoma]

bw, body weight; d, day; F, female; M, male; mo, month; NR, not reported; NS, not significant; wk, week; yr, year

males ($P = 0.016$) and of thyroid follicular cell adenoma in females ($P = 0.031$). [The Working Group noted that there was no apparent progression to carcinoma for either tumour type.]

The EPA (1991a, b, c, d) provided information on another long-term study in which groups of 50 male and 50 female Sprague-Dawley rats [age at start not reported] were given diets containing glyphosate (purity, 98.7%) at a concentration of 0, 30 (3 mg/kg bw per day), 100 (10 mg/kg bw per day), or 300 ppm (31 mg/kg bw per day), ad libitum, for life (up to 26 months). No information was provided on body weight or survival of the study animals. An increase in the incidence of pancreatic islet cell adenoma was reported in males at the lowest dose: controls, 0/50 (0%); lowest dose, 5/49 (10%) [$P < 0.05$; Fisher exact test]; intermediate dose, 2/50 (4%); highest dose, 2/50 (4%). [The Working Group noted that there was no statistically significant positive dose-related trend in the incidence of these tumours, and no apparent progression to carcinoma.]

3.2.3 Review articles

Greim *et al.* (2015) have published a review article containing information on nine long-term bioassay feeding studies in rats. Of these studies, two had been submitted for review to the EPA (1991a, b, c, d), two to the JMPR (JMPR, 2006), and one had been published in the openly available scientific literature (Chruscielska *et al.*, 2000); these studies are discussed earlier in Section 3.2. The review article reported on an additional four long-term bioassay studies in rats that had not been previously published, but had been submitted to various organizations for registration purposes. The review article provided a brief summary of each study and referred to an online data supplement containing the original data on tumour incidence from study reports. The four additional long-term bioassay studies in rats are summarized below. [The Working Group did not evaluate these studies, which are not included in Table 3.2 and Section 5.3, because the information provided in the review article and its supplement was insufficient (e.g. information lacking on statistical methods, choice of doses, body-weight gain, survival data, details on histopathological examination and/or stability of dosed feed mixture).]

In one study (identified as Study 4, 1996), groups of 50 male and 50 female Wistar rats [age at start not reported] were given diets containing glyphosate (purity, 96%) at a concentration of 0, 100, 1000, or 10 000 ppm, ad libitum, for 24 months. It was reported that hepatocellular adenomas and hepatocellular carcinomas were found at non-statistically significant incidences in both males and females. There was no significant increase in tumour incidence in the treated groups. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In one study in Sprague-Dawley rats (identified as Study 5, 1997), groups of 50 male and 50 female rats [age at start not reported] were given diets containing glyphosate technical acid [purity not reported] at a concentration of 0, 3000, 15 000, or 25 000 ppm, ad libitum, for 24 months. There was no significant increase in tumour incidence in the treated groups. [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information.]

In a second study in Sprague Dawley rats (identified as Study 6, 1997b), groups of 50 males and 50 females [age at start not reported] were given diets containing glyphosate (purity, 94.6–97.6%) at a concentration of 0, 3000, 10 000, or 30 000 ppm, ad libitum, for 24 months. Non-significant increases in tumour incidences compared with controls were noted for skin keratoacanthoma in males at the highest dose, and for fibroadenoma of the mammary gland in females at the lowest and intermediate doses. [The Working Group was unable to evaluate this

study because of the limited experimental data provided in the review article and supplemental information.]

In another study in male and female Wistar rats (identified as Study 8, 2009b), groups of 51 male and 51 female rats [age at start not reported] were fed diets containing glyphosate (purity, 95.7%) at a concentration of 0, 1500, 5000, or 15 000 ppm, ad libitum, for 24 months. The highest dose was progressively increased to reach 24 000 ppm by week 40. A non-significant increase in tumour incidence was noted for adenocarcinoma of the mammary gland in females at the highest dose (6/51) compared with controls (2/51). [The Working Group was unable to evaluate this study because of the limited experimental data provided in the review article and supplemental information. The Working Group noted that tumours of the mammary gland had been observed in other studies in rats reviewed for the present *Monograph*.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

4.1.1 Introduction

The herbicidal activity of glyphosate is attributed to interference with the production of essential aromatic amino acids (EPA, 1993b). In plants, glyphosate competitively inhibits the activity of enolpyruvylshikimate phosphate synthase, an enzyme that is not present in mammalian cells. Glyphosate is degraded by soil microbes to aminomethylphosphonic acid (AMPA) (see Fig. 4.1), a metabolite that can accumulate in the environment. In mammals, glyphosate is not metabolized efficiently and is mainly excreted unchanged into the urine; however, it has been suggested that glyphosate can undergo gut microbial metabolism in humans (Motojyuku *et al.*, 2008) and rodents (Brewster *et al.*, 1991).

4.1.2 Absorption

(a) Humans

Data on the absorption of glyphosate via intake of food and water in humans were not available to the Working Group. Inhalation of glyphosate is considered to be a minor route of exposure in humans, because glyphosate is usually formulated as an isopropylamine salt with a very low vapour pressure (Tomlin, 2000).

In the Farm Family Exposure Study, 60% of farmers had detectable levels of glyphosate in 24-hour composite urine samples taken on the day they had applied a glyphosate-based formulation (Acquavella *et al.*, 2004). Farmers who did not use rubber gloves had higher urinary concentrations of glyphosate than those who did use gloves [indicating that dermal absorption is a relevant route of exposure]. In a separate study, detectable levels of glyphosate were found in urine samples from farm families and non-farm families (Curwin *et al.*, 2007).

In accidental and deliberate intoxication cases involving ingestion of glyphosate-based formulations, glyphosate was readily detectable in the blood (Zouaoui *et al.*, 2013). After deliberate or accidental ingestion, one glyphosate-based formulation was found to be more lethal to humans than another (Sørensen & Gregersen, 1999). [Greater lethality was attributed to the presence of trimethylsulfonium counterion, which might facilitate greater absorption after oral exposure.]

Small amounts of glyphosate can be absorbed after dermal exposures in humans in vitro. For example, when an aqueous solution of 1% glyphosate was applied in an in-vitro human skin model, only 1.4% of the applied dose was absorbed through the skin. Glyphosate is typically formulated as an isopropylamine salt, and is dissolved in a water-based vehicle, while the

stratum corneum is a lipid-rich tissue (Wester *et al.*, 1991). In-vitro studies using human skin showed that percutaneous absorption of a glyphosate-based formulation was no more than 2% of the administered dose over a concentration range of 0.5–154 µg/cm^2 and a topical volume range of 0.014–0.14 mL/cm^2. In addition, very little glyphosate (≤ 0.05% of the administered dose) was sequestered in the stratum corneum after dermal application (Wester *et al.*, 1991).

In the human Caco-2 cell line, an in-vitro model of intestinal enterocytes, glyphosate (> 10 mg/mL) was shown to significantly disrupt barrier properties, leading to an increase in paracellular permeability (transport of substances that pass through the intercellular space between the cells) (Vasiluk *et al.*, 2005).

(b) Experimental systems

Three studies have been conducted to investigate the absorption of a single oral dose of glyphosate in rats (Brewster *et al.*, 1991; Chan & Mahler, 1992; EPA, 1993b).

In male Sprague-Dawley rats given [^{14}C]-labelled glyphosate (10 mg/kg bw), the majority of the radiolabel was associated with the gastrointestinal contents and small intestinal tissue 2 hours after administration (Brewster *et al.*, 1991). Approximately 35–40% of the administered dose was found to be absorbed from the gastrointestinal tract. Urinary and faecal routes of elimination were equally important. [The Working Group concluded that glyphosate is incompletely absorbed from the gastrointestinal tract after oral exposure in rats.]

In a study by the United States National Toxicology Programme (NTP) in Fisher 344 rats, 30% of the administered oral dose (5.6 mg/kg bw) was absorbed, as determined by urinary excretion data (Chan & Mahler, 1992). This finding was in accordance with the previously described study of oral exposure in rats (Brewster *et al.*, 1991).

In a study reviewed by the EPA, Sprague-Dawley rats were given an oral dose of glyphosate (10 mg/kg bw); 30% and 36% of the administered dose was absorbed in males and females, respectively (EPA, 1993b). At a dose that was ~10-fold higher (1000 mg/kg bw), oral absorption of glyphosate by the rats was slightly reduced.

In a 14-day feeding study in Wistar rats given glyphosate at dietary concentrations of up to 100 ppm, only ~15% of the administered dose was found to be absorbed (JMPR, 2006). In New Zealand White rabbits or lactating goats given glyphosate as single oral doses (6–9 mg/kg bw), a large percentage of the administered dose was recovered in the faeces [suggesting very poor gastrointestinal absorption of glyphosate in these animal models] (JMPR, 2006).

In monkeys given glyphosate by dermal application, percutaneous absorption was estimated to be between 1% and 2% of the administered dose (Wester *et al.*, 1991). Most of the administered dose was removed by surface washes of the exposed skin.

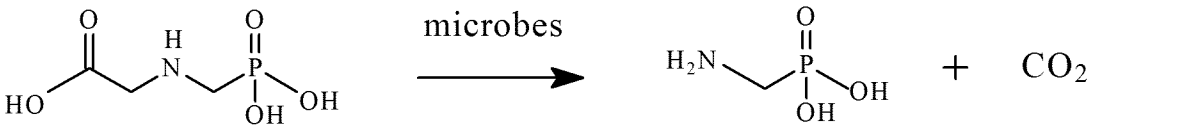
4.1.3 Distribution

(a) Humans

No data in humans on the distribution of glyphosate in systemic tissues other than blood were available to the Working Group. In cases of accidental or deliberate intoxication involving ingestion of glyphosate-based formulations, glyphosate was measured in blood. Mean blood concentrations of glyphosate were 61 mg/L and 4146 mg/L in mild-to-moderate cases of intoxication and in fatal cases, respectively (Zouaoui *et al.*, 2013).

One report, using optical spectroscopy and molecular modelling, indicated that glyphosate could bind to human serum albumin, mainly by hydrogen bonding; however, the fraction of glyphosate that might bind to serum proteins in blood was not actually measured (Yue *et al.*, 2008).

Fig. 4.1 Microbial metabolism of glyphosate to AMPA



Glyphosate is degraded to AMPA by microbial metabolism
Compiled by the Working Group

(b) Experimental systems

In Sprague-Dawley rats given a single oral dose of glyphosate (100 mg/kg bw), glyphosate concentrations in plasma reached peak levels, then declined slowly from day 1 to day 5 (Bernal *et al.*, 2010). The plasma data appeared to fit a one-compartment model with an elimination rate constant of k_{el} = 0.021 hour^{-1}. [The Working Group estimated the elimination half-life of glyphosate to be 33 hours.] Tissue levels of glyphosate were not determined in this study. In a study by Brewster *et al.* (1991), the tissue levels of glyphosate at 2, 6.3, 28, 96, and 168 hours in Sprague-Dawley rats given a single oral dose (10 mg/kg bw) declined rapidly. Tissues with the greatest amounts of detectable radiolabel (> 1% of the administered dose) were the small intestine, colon, kidney, and bone. Peak levels were reached in small intestine tissue and blood by 2 hours, while peak levels in other tissues occurred at 6.3 hours after dosing. After 7 days, the total body burden of [^{14}C]-labelled residues was ~1% of the administered dose, and was primarily associated with the bone (~1 ppm). In every tissue examined after administration of [^{14}C]-labelled glyphosate, essentially 100% of the radiolabel that was present in the tissue was unmetabolized parent glyphosate. Thus, essentially 100% of the body burden was parent compound, with no significant persistence of glyphosate after 7 days (Brewster *et al.*, 1991). In a 14-day feeding study in Wistar rats given diets containing glyphosate at 100 ppm, glyphosate reached steady-state levels in the blood by day 6 (JMPR, 2006). The tissue concentrations of glyphosate had the following rank order: kidneys > spleen > fat > liver. Tissue levels declined rapidly after cessation of exposure to glyphosate. A second study in rats given glyphosate (10 mg/kg bw per day, 14 days) followed by a single oral dose of [^{14}C]-glyphosate (at 10 mg/kg bw) showed that repeated dosing did not alter the tissue distribution of glyphosate (JMPR, 2006).

In rhesus monkeys, tissues harvested 7 days after dermal exposures to [^{14}C]-labelled glyphosate did not contain radiolabel at detectable levels (Wester *et al.*, 1991).

4.1.4 Metabolism and modulation of metabolic enzymes

(a) Metabolism

Glyphosate is degraded in the environment by soil microbes, primarily to AMPA and carbon dioxide (Fig. 4.1; Jacob *et al.*, 1988). A minor pathway for the degradation of glyphosate in bacteria (*Pseudomonas sp.* strain LBr) is via conversion to glycine (Jacob *et al.*, 1988). In a case of deliberate poisoning with a glyphosate-based formulation, small amounts of AMPA (15.1 µg/mL) were detectable in the blood (Motojyuku *et al.*, 2008) [suggesting that this pathway might also operate in humans]. In rats given a single high oral dose of glyphosate (100 mg/kg bw), small amounts of AMPA were detected in the plasma (Bernal *et al.*, 2010). In

male Sprague-Dawley rats given an oral dose of glyphosate (10 mg/kg bw), a very small amount of AMPA (< 0.04% of the administered dose) was detected in the colon 2 hours after dosing; this was attributed to intestinal microbial metabolism (Brewster *et al.*, 1991).

(b) Modulation of metabolic enzymes

(i) Humans

In human hepatic cell lines, treatment with one of four glyphosate-based formulations produced by the same company was shown to enhance CYP3A4 and CYP1A2 levels, while glutathione transferase levels were reduced (Gasnier *et al.*, 2010). [The Working Group noted that it was not clear whether the effects were caused by glyphosate alone or by the adjuvants contained in the formulation.]

(ii) Experimental systems

Exposure of Wistar rats to a glyphosate-based formulation significantly altered some hepatic xenobiotic enzyme activities (Larsen *et al.*, 2014). Liver microsomes obtained from male and female rats treated with the formulation exhibited ~50% reductions in cytochrome P450 (CYP450) content compared with control (untreated) rats. However, opposing effects were observed when assessing 7-ethoxycoumarin *O*-deethylase activity (7-ECOD, a non-specific CYP450 substrate). Female rats treated with the glyphosate-based formulation exhibited a 57% increase in hepatic microsomal 7-ECOD activity compared with controls, while male rats treated with the formulation exhibited a 58% decrease in this activity (Larsen *et al.*, 2014). [The Working Group noted that it was not clear whether the effects were caused by glyphosate alone or by adjuvants contained in the formulation.]

4.1.5 Excretion

(a) Humans

Excretion of glyphosate in humans was documented in several biomonitoring studies. For example, as part of the Farm Family Exposure Study, urinary concentrations of glyphosate were evaluated immediately before, during, and after glyphosate application in 48 farmers and their spouses and children (Acquavella *et al.*, 2004). Dermal contact with glyphosate during mixing, loading, and application was considered to be the main route of exposure in the study. On the day the herbicide was applied, 60% of the farmers had detectable levels of glyphosate in 24-hour composite urine samples, as did 4% of their spouses and 12% of children. For farmers, the geometric mean concentration was 3 µg/L, the maximum value was 233 µg/L, and the highest estimated systemic dose was 0.004 mg/kg bw (Acquavella *et al.*, 2004). In a separate study, detectable levels of glyphosate were excreted in the urine of members of farm families and of non-farm families, with geometric means ranging from 1.2 to 2.7 µg/L (Curwin *et al.*, 2007).

In a study of a rural population living near areas sprayed for drug eradication in Colombia (see Section 1.4.1, Table 1.5), mean urinary glyphosate concentrations were 7.6 µg/L (range, undetectable to 130 µg/L) (Varona *et al.*, 2009). AMPA was detected in 4% of urine samples (arithmetic mean, 1.6 µg/L; range, undetectable to 56 µg/L).

(b) Experimental systems

In an NTP study in Fisher 344 rats given a single oral dose of [^{14}C]-labelled glyphosate (5.6 or 56 mg/kg bw), it was shown that > 90% of the radiolabel was eliminated in the urine and faeces within 72 hours (Chan & Mahler, 1992). In Sprague-Dawley rats given [^{14}C]-labelled glyphosate at an oral dose of 10 or 1000 mg/kg bw, ~60–70% of the administered dose was excreted in the faeces, and the remainder in the urine (EPA,

1993b). By either route, most (98%) of the administered dose was excreted as unchanged parent compound. AMPA was the only metabolite found in the urine (0.2–0.3% of the administered dose) and faeces (0.2–0.4% of the administered dose). [The large amount of glyphosate excreted in the faeces is consistent with its poor oral absorption.] Less than 0.3% of the administered dose was expired as carbon dioxide.

In rhesus monkeys given glyphosate as an intravenous dose (9 or 93 µg), > 95% of the administered dose was excreted in the urine (Wester *et al.*, 1991). Nearly all the administered dose was eliminated within 24 hours. In contrast, in rhesus monkeys given glyphosate by dermal application (5400 µg/20 cm ^{2}), only 2.2% of the administered dose was excreted in the urine within 7 days (Wester *et al.*, 1991).

Overall, systemically absorbed glyphosate is not metabolized efficiently, and is mainly excreted unchanged into the urine.

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

Glyphosate has been studied for genotoxic potential in a wide variety of assays. Studies carried out in exposed humans, in human cells in vitro, in other mammals in vivo and in vitro, and in non-mammalian systems in vivo and in vitro, respectively, are summarized in Table 4.1, Table 4.2, Table 4.3, Table 4.4, and Table 4.5. [A review article by Kier & Kirkland (2013) summarized the results of published articles and unpublished reports of studies pertaining to the genotoxicity of glyphosate and glyphosate formulations. A supplement to this report contained information on 66 unpublished regulatory studies. The conclusions and data tables for each individual study were included in the supplement; however, the primary study reports from which these data were extracted were not available to the Working Group. The information provided in the supplement was insufficient regarding topics such as details of statistical methods, choice of the highest dose tested, and verification of the target tissue exposure. The Working Group determined that the information in the supplement to Kier & Kirkland (2013) did not meet the criteria for data inclusion as laid out in the Preamble to the *IARC Monographs*, being neither "reports that have been published or accepted for publication in the openly available scientific literature" nor "data from governmental reports that are publicly available" (IARC, 2006). The review article and supplement were not considered further in the evaluation.]

(a) Humans

(i) Studies in exposed humans

See Table 4.1

In exposed individuals (n = 24) living in northern Ecuador in areas sprayed with a glyphosate-based formulation, a statistically significant increase in DNA damage (DNA strand breaks) was observed in blood cells collected 2 weeks to 2 months after spraying (Paz-y-Miño *et al.*, 2007). The same authors studied blood cells from individuals (n = 92) in 10 communities in Ecuador's northern border, who were sampled 2 years after the last aerial spraying with a herbicide mix containing glyphosate, and showed that their karyotypes were normal compared with those of a control group (Paz-y-Miño *et al.*, 2011).

Bolognesi *et al.* (2009) studied community residents (137 women of reproductive age and their 137 spouses) from five regions in Colombia. In three regions with exposures to glyphosate-based formulations from aerial spraying, blood samples were taken from the same individuals at three time-points (before spraying (baseline), 5 days after spraying and 4 months after spraying) to determine the frequency of micronucleus formation in lymphocytes. The baseline frequency of binucleated cells with micronuclei was significantly higher in subjects

from the three regions where there had been aerial spraying with glyphosate-formulations and in a fourth region with pesticide exposure (but not through aerial spraying), compared with a reference region (without use of pesticide). The frequency of micronucleus formation in peripheral blood lymphocytes was significantly increased, compared with baseline levels in the same individuals, after aerial spraying with glyphosate-based formulations in each of the three regions (see Table 4.1 ; Bolognesi *et al.*, 2009). Immediately after spraying, subjects who reported direct contact with the glyphosate-based spray showed a higher frequency of binucleated cells with micronuclei. However, the increase in frequency of micronucleus formation observed immediately after spraying was not consistent with the rates of application used in the regions, and there was no association between self-reported direct contact with pesticide sprays and frequency of binucleated cells with micronuclei. In subjects from one but not other regions, the frequency of binucleated cells with micronuclei was significantly decreased 4 months after spraying, compared with immediately after spraying.

(ii) Human cells in vitro

See Table 4.2

Glyphosate induced DNA strand breaks (as measured by the comet assay) in liver Hep-2 cells (Mañas *et al.*, 2009a), lymphocytes (Mladinic *et al.*, 2009b; Alvarez-Moya *et al.*, 2014), GM38 fibroblasts, the HT1080 fibrosarcoma cell line (Monroy *et al.*, 2005), and the TR146 buccal carcinoma line (Koller *et al.*, 2012). DNA strand breaks were induced by AMPA in Hep-2 cells (Mañas *et al.*, 2009b), and by a glyphosate-based formulation in the TR146 buccal carcinoma cell line (Koller *et al.*, 2012).

In human lymphocytes, AMPA (Mañas *et al.*, 2009b), but not glyphosate (Mañas *et al.*, 2009a), produced chromosomal aberrations. Glyphosate did not induce a concentration-related increase in micronucleus formation in human lymphocytes at levels estimated to correspond to occupational and residential exposure (Mladinic *et al.*, 2009a). Sister-chromatid exchange was induced by glyphosate (Bolognesi *et al.*, 1997), and by a glyphosate-based formulation (Vigfusson & Vyse, 1980; Bolognesi *et al.*, 1997) in human lymphocytes exposed in vitro.

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.3

The ability of glyphosate or a glyphosate-based formulation to induce DNA adducts was studied in mice given a single intraperitoneal dose. Glyphosate induced DNA adducts (8-hydroxy deoxyguanosine) in the liver, but not in the kidney, while a glyphosate-based formulation caused a slight increase in DNA adducts in the kidney, but not in the liver (Bolognesi *et al.*, 1997). Peluso *et al.* (1998) showed that a glyphosate-based formulation (glyphosate, 30.4%), but not glyphosate alone, caused DNA adducts (as detected by ^{32}P-DNA post-labelling) in mouse liver and kidney. Glyphosate and a glyphosate-based formulation produced DNA strand breaks in the liver and kidney after a single intraperitoneal dose (Bolognesi *et al.*, 1997).

In mice given a single dose of glyphosate by gavage, no genotoxic effect was observed by the dominant lethal test (EPA, 1980a).

After a single intraperitoneal dose, no chromosomal aberrations were observed in the bone marrow of rats treated with glyphosate (Li & Long, 1988), while chromosomal aberrations were increased in the bone marrow of mice given a glyphosate-based formulation (glyphosate isopropylamine salt, ~41%) (Prasad *et al.*, 2009). A single oral dose of a glyphosate-based formulation did not cause chromosomal aberrations in mice (Dimitrov *et al.*, 2006).

In mice treated by intraperitoneal injection, a single dose of glyphosate did not cause

Table 4.1 Genetic and related effects of glyphosate in exposed humans

Tissue	Cell type (if specified)	End-point	Test	Description of exposure and controls	Response[a]/ significance	Comments	Reference
Blood	NR	DNA damage	DNA strand breaks, comet assay	24 exposed individuals in northern Ecuador; areas sprayed with glyphosate-based formulation (sampling 2 weeks to 2 months after spraying); control group was 21 non-exposed individuals	+ $P < 0.001$		Paz-y-Miño *et al.* (2007)
Blood	NR	Chromosomal damage	Chromosomal aberrations	92 individuals in 10 communities, northern border of Ecuador; sampling 2 years after last aerial spraying with herbicide mix containing glyphosate); control group was 90 healthy individuals from several provinces without background of smoking or exposure to genotoxic substances (hydrocarbons, X-rays, or pesticides)	–	182 karyotypes were considered normal [Smoking status, NR]	Paz-y-Miño *et al.* (2011)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	55 community residents, Nariño, Colombia; area with aerial glyphosate-based formulation spraying for coca and poppy eradication (glyphosate was tank-mixed with an adjuvant)	+ [$P < 0.001$]	*P* values for after spraying vs before spraying in the same individuals	Bolognesi *et al.* (2009)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	53 community residents, Putumayo, Colombia; area with aerial glyphosate-based formulation spraying for coca and poppy eradication (glyphosate was tank-mixed with an adjuvant)	+ [$P = 0.01$]	*P* values for after spraying vs before spraying in the same individuals	Bolognesi *et al.* (2009)
Blood	Lymphocytes	Chromosomal damage	Micronucleus formation	27 community residents, Valle del Cauca, Colombia; area where glyphosate-based formulation was applied through aerial spraying for sugar-cane maturation (glyphosate was applied without adjuvant)	+ [$P < 0.001$]	*P* values for after spraying vs before spraying in the same individuals	Bolognesi *et al.* (2009)

[a] +, positive; –, negative
NR, not reported; vs, versus

micronucleus formation in the bone marrow (Rank *et al.*, 1993), although two daily doses did (Bolognesi *et al.*, 1997; Mañas *et al.*, 2009a). AMPA, the main metabolite of glyphosate, also produced micronucleus formation after two daily intraperitoneal doses (Mañas *et al.*, 2009b). Conflicting results for micronucleus induction were obtained in mice exposed intraperitoneally to a glyphosate-based formulation. A single dose of the formulation at up to 200 mg/kg bw did not induce micronucleus formation in the bone marrow in one study (Rank *et al.* 1993), while it did increase micronucleus formation at 25 mg/kg bw in another study (Prasad *et al.*, 2009). After two daily intraperitoneal doses, a glyphosate-based formulation did not induce micronucleus formation at up to 200 mg/kg bw according to Grisolia (2002), while Bolognesi *et al.* (1997) showed that the formulation did induce micronucleus formation at 450 mg/kg bw. In mice given a single oral dose of a glyphosate-based formulation at 1080 mg/kg bw, no induction of micronuclei was observed (Dimitrov *et al.*, 2006).

(ii) Non-human mammalian cells in vitro

See Table 4.4

Glyphosate did not induce unscheduled DNA synthesis in rat primary hepatocytes, or *Hprt* mutation (with or without metabolic activation) in Chinese hamster ovary cells (Li & Long, 1988).

In bovine lymphocytes, chromosomal aberrations were induced by glyphosate in one study (Lioi *et al.*, 1998), but not by a glyphosate formulation in another study (Siviková & Dianovský, 2006). Roustan *et al.* (2014) demonstrated, in the CHO-K1 ovary cell line, that glyphosate induced micronucleus formation only in the presence of metabolic activation, while AMPA induced micronucleus formation both with and without metabolic activation. Sister-chromatid exchange was observed in bovine lymphocytes exposed to glyphosate (Lioi *et al.*, 1998) or a glyphosate formulation (in the absence but not the presence of metabolic activation) (Siviková & Dianovský, 2006).

(iii) Non-mammalian systems in vivo

See Table 4.5

Fish and other species

In fish, glyphosate produced DNA strand breaks in the comet assay in sábalo (Moreno *et al.*, 2014), European eel (Guilherme *et al.*, 2012b), zebrafish (Lopes *et al.*, 2014), and Nile tilapia (Alvarez-Moya *et al.*, 2014). AMPA also induced DNA strand breaks in the comet assay in European eel (Guilherme *et al.*, 2014b). A glyphosate-based formulation produced DNA strand breaks in numerous fish species, such as European eel (Guilherme *et al.*, 2010, 2012b, 2014a; Marques *et al.*, 2014, 2015), sábalo (Cavalcante *et al.*, 2008; Moreno *et al.*, 2014), guppy (De Souza Filho *et al.*, 2013), bloch (Nwani *et al.*, 2013), neotropical fish *Corydoras paleatus* (de Castilhos Ghisi & Cestari, 2013), carp (Gholami-Seyedkolaei *et al.*, 2013), and goldfish (Cavaş & Könen, 2007).

AMPA, the main metabolite of glyphosate, induced erythrocytic nuclear abnormalities (kidney-shaped and lobed nuclei, binucleate or segmented nuclei and micronuclei) in European eel (Guilherme *et al.*, 2014b). Micronucleus formation was induced by different glyphosate-based formulations in various fish(Grisolia, 2002; Cavaş & Könen, 2007; De Souza Filho *et al.*, 2013; Vera-Candioti *et al.*, 2013).

Glyphosate-based formulations induced DNA strand breaks in other species, including caiman (Poletta *et al.*, 2009), frog (Meza-Joya *et al.*, 2013), tadpoles (Clements *et al.*, 1997), and snail (Mohamed, 2011), but not in oyster (Akcha *et al.*, 2012), clam (dos Santos & Martinez, 2014), and mussel glochidia (Conners & Black, 2004). In earthworms, one glyphosate-based formulation induced DNA strand breaks while two others did not (Piola *et al.*, 2013; Muangphra *et al.*, 2014), highlighting the potential importance of components other than the active ingredient in the formulation.

Table 4.2 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in human cells in vitro

Tissue, cell line	End-point	Test	Results[a]		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Glyphosate							
Liver Hep-2	DNA damage	DNA strand breaks, comet assay	+	NT	3 mM [507.2 µg/mL]	$P < 0.01$; dose–response relationship ($r \geq 0.90$; $P < 0.05$)	Mañas et al. (2009a)
Lymphocytes	DNA damage	DNA strand breaks, standard and hOGG1 modified comet assay	+	+	3.5 µg/mL	With the hOGG1 modified comet assay, + S9, the increase was significant ($P < 0.01$) only at the highest dose tested (580 µg/mL)	Mladinic et al. (2009b)
Lymphocytes	DNA damage	DNA strand breaks, comet assay	+	NT	0.0007 mM [0.12 µg/mL]	$P \leq 0.01$	Alvarez-Moya et al. (2014)
Fibroblast GM 38	DNA damage	DNA strand breaks, comet assay	+	NT	4 mM [676 µg/mL]	$P < 0.001$	Monroy et al. (2005)
Fibroblast GM 5757	DNA damage	DNA strand breaks, comet assay	(+)	NT	75 mM [12 680 µg/mL]	Glyphosate (ineffective alone, data NR) increased strand breaks induced by H_2O_2 (40 or 50 µM) ($P < 0.004$ vs H_2O_2 alone)	Lioi et al. (2004)
Fibrosarcoma HT1080	DNA damage	DNA strand breaks, comet assay	+	NT	4.75 mM [803 µg/mL]	$P < 0.001$	Monroy et al. (2005)
Buccal carcinoma TR146	DNA damage	DNA strand breaks, SCGE assay	+	NT	20 µg/mL	Dose-dependent increase ($P \leq 0.05$)	Koller et al. (2012)
Lymphocytes	Chromosomal damage	Chromosomal aberrations	–	NT	6 mM [1015 µg/mL]		Mañas et al. (2009a)
Lymphocytes	Chromosomal damage	Micronucleus formation	–	(+)	580 µg/mL	$P < 0.01$ at the highest exposure + S9 No concentration-related increase in micronuclei containing the centromere signal (C+)	Mladinic et al. (2009a)

Table 4.2 (continued)

Tissue, cell line	End-point	Test	Results[a]		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	1000 µg/mL	$P < 0.05$	Bolognesi *et al.* (1997)
AMPA							
Liver Hep-2	DNA damage	DNA strand breaks, comet assay	+	NT	4.5 mM [500 µg/mL]	$P < 0.05$ at 4.5 mM; $P < 0.01$ at up to 7.5 mM Dose–response relationship ($r \geq 0.90$; $P < 0.05$)	Mañas *et al.* (2009b)
Lymphocytes	Chromosomal damage	Chromosomal aberrations	+	NT	1.8 mM [200 µg/mL]	$P < 0.05$	Mañas *et al.* (2009b)
Glyphosate-based formulations							
Liver HepG2	DNA damage	DNA strand breaks, comet assay	(+)	NT	5 ppm	Glyphosate, 400 g/L Dose-dependent increase, greatest increase at 10 ppm Statistical analysis, NR	Gasnier *et al.* (2009)
Buccal carcinoma TR146	DNA damage	DNA strand breaks, SCGE assay	+	NT	20 µg/mL	Glyphosate acid, 450g/L Dose-dependent increase ($P \leq 0.05$)	Koller *et al.* (2012)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	250 µg/mL	$P < 0.001$ No growth at 25 mg/mL	Vigfusson & Vyse (1980)
Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	100 µg/mL	Glyphosate, 30.4% $P < 0.05$	Bolognesi *et al.* (1997)

[a] +, positive; -, negative; (+) or (-) positive/negative in a study with limited quality

AMPA, aminomethyl phosphonic acid; HID, highest ineffective dose; hOGG1, human 8-hydroxyguanosine DNA-glycosylase; LED, lowest effective dose; NR, not reported; NT, not tested; S9, 9000 × *g* supernatant; SCGE, single cell gel electrophoresis; vs, versus

Micronucleus formation was induced by a glyphosate-based formulation (glyphosate, 36%) in earthworms (Muangphra *et al.*, 2014), and by a different glyphosate-based formulation in caiman (Poletta *et al.*, 2009, 2011), and frog (Yadav *et al.*, 2013).

Insects

In standard *Drosophila melanogaster*, glyphosate induced mutation in the test for somatic mutation and recombination, but not in a cross of flies characterized by an increased capacity for CYP450-dependent bioactivation (Kaya *et al.*, 2000). A glyphosate-based formulation also caused sex-linked recessive lethal mutations in *Drosophila* (Kale *et al.*, 1995).

Plants

In plants, glyphosate produced DNA damage in *Tradescantia* in the comet assay (Alvarez-Moya *et al.*, 2011). Chromosomal aberration was induced after exposure to glyphosate in fenugreek (Siddiqui *et al.*, 2012), and in onion in one study (Frescura *et al.*, 2013), but not in another (Rank *et al.*, 1993). A glyphosate-based formulation also induced chromosomal aberration in barley roots (Truta *et al.*, 2011) and onion (Rank *et al.*, 1993), but not in *Crepis capillaris* (hawksbeard) (Dimitrov *et al.*, 2006). Micronucleus formation was not induced by glyphosate in *Vicia faba* bean (De Marco *et al.*, 1992) or by a glyphosate-based formulation in *Crepis capillaris* (Dimitrov *et al.*, 2006).

(iv) Non-mammalian systems in vitro

See Table 4.6

Glyphosate induced DNA strand breaks in erythrocytes of tilapia fish, as demonstrated by comet assay (Alvarez-Moya *et al.*, 2014).

Glyphosate did not induce mutation in *Bacillus subtillis*, *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, or in *Escherichia coli* WP2, with or without metabolic activation (Li & Long, 1988). However, Rank *et al.* (1993) demonstrated that a glyphosate-based formulation was mutagenic in *S. typhimurium* TA98 in the absence of metabolic activation, and in *S. typhimurium* TA100 in the presence of metabolic activation.

4.2.2 Receptor-mediated mechanisms

(a) Sex-hormone pathway disruption

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

In hormone-dependent T47D breast cancer cells, the proliferative effects of glyphosate (10^{-6} to 1 µM) (see Section 4.2.4) and those of 17β-estradiol (the positive control) were mitigated by the estrogen receptor antagonist, ICI 182780; the proliferative effect of glyphosate was completely abrogated by the antagonist at a concentration of 10 nM (Thongprakaisang *et al.*, 2013). Glyphosate also induced activation of the estrogen response element (ERE) in T47D breast cancer cells that were stably transfected with a triplet ERE-promoter-luciferase reporter gene construct. Incubation with ICI 182780 at 10 nM eliminated the response. When the transfected cells were incubated with both 17β-estradiol and glyphosate, the effect of 17β-estradiol was reduced and glyphosate behaved as an estrogen antagonist. After 6 hours of incubation, glyphosate increased levels of estrogen receptors ERα and ERβ in a dose-dependent manner in T47D cells; after 24 hours, only ERβ levels were increased and only at the highest dose of glyphosate. [These findings suggested that the proliferative effects of glyphosate on T47D cells are mediated by ER.]

In human hepatocarcinoma HepG2 cells, four glyphosate-based formulations produced by the same company had a marked effect on the activity and transcription of aromatase, while glyphosate alone differed from controls, but not significantly so (Gasnier *et al.*, 2009).

Table 4.3 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in non-human mammals in vivo

Species, strain (sex)	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Glyphosate								
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA adducts, 8-OHdG by LC/UV	+	300 mg/kg bw	i.p.; 1×; sampled after 8 and 24 h	Single dose tested only $P < 0.05$ after 24 h	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA adducts, 8-OHdG by LC/UV	–	300 mg/kg bw	i.p.; 1×; sampled after 8 and 24 h	Single dose tested only	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M, F)	Kidney	DNA damage	DNA adducts, ^{32}P-DNA post labelling	–	270 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt	Peluso *et al.* (1998)
Mouse, Swiss CD1 (M, F)	Liver	DNA damage	DNA adducts, ^{32}P-DNA post labelling	–	270 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt	Peluso *et al.* (1998)
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA strand breaks, alkaline elution assay	+	300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Single dose tested only $P < 0.05$ after 4 h	Bolognesi *et al.* (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA strand breaks, alkaline elution assay	+	300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Single dose tested only $P < 0.05$ after 4 h	Bolognesi *et al.* (1997)
Mouse, CD-1 (M)	Uterus after mating	Mutation	Dominant lethal test	–	2000 mg/kg bw	Oral gavage; 1 ×	Proportion of early resorptions evaluated after mating of non-treated females with glyphosate-treated male mice	EPA (1990)
Rat, Sprague-Dawley (M, F)	Bone marrow	Chromosomal damage	Chromosomal aberrations	–	1000 mg/kg bw	i.p.; 1 ×; sampled after 6, 12 and 24 h	Single dose tested only	Li & Long (1988)
Mouse, NMRI-bom (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	–	200 mg/kg bw	i.p.; 1 ×; sampled after 24 and 48 h	Glyphosate isopropylamine salt	Rank *et al.* (1993)
Mouse, Swiss CD1 (M)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	300 mg/kg bw	i.p.; 2 × 150 mg/kg bw with 24 h interval; sampled 6 or 24 h after the last injection	Single dose tested only $P < 0.05$ after 24 h	Bolognesi *et al.* (1997)

Table 4.3 (continued)

Species, strain (sex)	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, Balb C (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	400 mg/kg bw	i.p.; one injection per 24 h, 2 × 200, sampled 24 h after the last injection	$P < 0.01$ at the highest dose (400 mg/kg bw)	Manas et al. (2009a)
AMPA								
Mouse, Balb C (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	200 mg/kg bw	i.p.; one injection per 24 h, 2 × 100, sampled 24 h after the last injection	$P < 0.01$ at the lowest dose (200 mg/kg bw)	Manas et al. (2009b)
Glyphosate-based formulations								
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA adducts, 8-OHdG by LC/UV	–	~300 mg/kg bw	i.p.; 1 ×, sampled after 8 and 24 h	Glyphosate, 30.4% Single dose tested only	Bolognesi et al. (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA adducts, 8-OHdG by LC/UV	+	~300 mg/kg bw	i.p.; 1 ×, sampled after 8 and 24 h	Glyphosate, 30.4% Single dose tested only $P < 0.05$	Bolognesi et al. (1997)
Mouse, Swiss CD1 (M, F)	Kidney	DNA damage	DNA adducts, ^{32}P-DNA post labelling	+	400 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt, 30.4%	Peluso et al. (1998)
Mouse, Swiss CD1 (M, F)	Liver	DNA damage	DNA adducts, ^{32}P-DNA post labelling	+	400 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt, 30.4%	Peluso et al. (1998)
Mouse, Swiss CD1 (M)	Liver	DNA damage	DNA strand breaks, alkaline elution assay	+	~300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Glyphosate, 30.4% Single dose tested only $P < 0.05$ only after 4 h	Bolognesi et al. (1997)
Mouse, Swiss CD1 (M)	Kidney	DNA damage	DNA strand breaks, alkaline elution assay	+	~300 mg/kg bw	i.p.; 1 ×; sampled after 4 and 24 h	Glyphosate, 30.4% Single dose tested only $P < 0.05$ only after 4 h	Bolognesi et al. (1997)
Mouse, C57BL (M)	Bone marrow (PCE)	Chromosomal damage	Chromosomal aberrations	–	1080 mg/kg bw	p.o. in distilled water; 1 ×; sampled after 6, 24, 48, 72, 96 and 120 h	Single dose tested only	Dimitrov et al. (2006)

Table 4.3 (continued)

Species, strain (sex)	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, Swiss albino (M)	Bone marrow	Chromosomal damage	Chromosomal aberrations	+	25 mg/kg bw	i.p.; 1 ×; sampled after 24, 48 and 72 h	Glyphosate isopropylamine salt, > 41% The percentage of aberrant cells was increased vs control in a dose- and time-dependent manner ($P < 0.05$)	Prasad et al. (2009)
Mouse, NMRI-bom (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	–	200 mg/kg bw	i.p.; 1 ×; sampled after 24 h	Glyphosate isopropylammonium salt, 480 g/L The percentage of PCE decreased	Rank et al. (1993)
Mouse, Swiss (M, F)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	–	200 mg/kg bw	i.p.; 2 × within 24 h interval and sampled 24 h after the last injection	Glyphosate isopropylammonium salt, 480 g/L	Grisolia (2002)
Mouse, Swiss albino (M)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	25 mg/kg bw	i.p.; 1 × ; sampled after 24, 48 and 72 h	Glyphosate isopropylamine salt, > 41% Significant induction of micronuclei vs control at both doses and all times ($P < 0.05$)	Prasad et al. (2009)
Mouse, Swiss CD1 (M)	Bone marrow (PCE)	Chromosomal damage	Micronucleus formation	+	450 mg/kg bw	i.p.; 2 × 225 mg/kg with 24 h interval; sampled 6 or 24 h after the last injection	Glyphosate, 30.4% Single dose tested only $P < 0.05$ after 6 h and 24 h	Bolognesi et al. (1997)
Mouse, C57BL (M)	Bone marrow	Chromosomal damage	Micronucleus formation	–	1080 mg/kg bw	p.o. in distilled water; 1 × ; sampled after 24, 48, 72, 96 and 120 h	Single dose tested only	Dimitrov et al. (2006)

[a] +, positive; -, negative; (+) or (-) positive/negative in a study with limited quality

bw, body weight; F, female; h, hour; HID, highest effective dose; i.p., intraperitoneal; LC, liquid chromatography; LED, lowest effective dose; M, male; PCE, polychromatic erythrocytes; p.o., oral; 8-OHdG, 8-hydroxydeoxyguanosine; UV, ultraviolet

Table 4.4 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in non-human mammalian cells in vitro

Species	Tissue, cell line	End-point	Test	Results[a]		Dose (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Glyphosate								
Rat, Fisher F334	Hepatocytes	DNA damage	Unscheduled DNA synthesis	–	NT	125 µg/mL		Li & Long (1988)
Hamster, Chinese	CHO-K_1BH_4 ovary, cell line	Mutation	*Hprt* mutation	–	–	22 500 µg/mL		Li & Long (1988)
Bovine	Lymphocytes	Chromosomal damage	Chromosomal aberrations	+	NT	17 µM [3 µg/mL]	$P < 0.05$	Lioi *et al.* (1998)
Hamster, Chinese	CHO-K1 ovary cell line	Chromosomal damage	Micronucleus formation	–	+	10 µg/mL	$P \leq 0.001$, in the dark +S9 Negative –S9 in the dark or with light irradiation	Roustan *et al.* (2014)
Bovine	Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	NT	17 µM [3 µg/mL]	$P < 0.05$	Lioi *et al.* (1998)
AMPA								
Hamster, Chinese	CHO-K1 ovary cell line	Chromosomal damage	Micronucleus formation	+	+	0.01 µg/mL	$P \leq 0.05$, in the dark –S9 Highest increase was observed at very low dose (0.0005 µg/mL) –S9 but with light-irradiation ($P < 0.01$)	Roustan *et al.* (2014)
Glyphosate-based formulations								
Bovine	Lymphocytes	Chromosomal damage	Chromosomal aberrations	–	NT	1120 µM [190 µg/mL]	Glyphosate, 62%	Siviková & Dianovský (2006)
Bovine	Lymphocytes	Chromosomal damage	Sister-chromatid exchange	+	–	56 µM [9.5 µg/mL]	Glyphosate, 62% Time of exposure, 24 h $P < 0.01$, –S9, at ≥ 56 µM	Siviková & Dianovský (2006)

[a] +, positive; –, negative; (+), weakly positive

AMPA, aminomethyl phosphonic acid; HIC, highest ineffective concentration; *Hprt*, hypoxanthine guanine phosphoribosyl transferase gene; LEC, lowest effective concentration; NT, not tested

Table 4.5 Genetic and related effects of glyphosate, AMPA, and glyphosate-based formulations in non-mammalian systems in vivo

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Glyphosate							
Fish	*Prochilodus lineatus* (sábalo), erythrocytes and gill cells	DNA damage	DNA strand breaks, comet assay	+	0.48 mg/L	Time of exposure 6, 24, and 96 h For erythrocytes, $P = 0.01$ after 6 h, and $P = 0.014$ after 96 h; no significant increase after 24 h For gill cells, $P = 0.02$ only after 6 h at 2.4 mg/L	Moreno *et al.* (2014)
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay	+	0.0179 mg/L	Time of exposure 1 and 3 days $P < 0.05$	Guilherme *et al.* (2012b)
Fish	*Danio rerio* (zebrafish), sperm	DNA damage	DNA strand breaks, acridine orange method	+	10 mg/L	After 96 h, DNA integrity was 78.3 ± 3.5%, significantly reduced from control (94.7 ± 0.9%) and 5 mg/L (92.6 ± 1.9%), ($P < 0.05$)	Lopes *et al.* (2014)
Fish	*Oreochromis niloticus* (Nile tilapia) branchial erythrocytes	DNA damage	DNA strand breaks, comet assay	+	7 µM [1.2 mg/L]	Time of exposure, 10 days $P < 0.001$ with concentrations ≥ 7 µM	Alvarez-Moya *et al.* (2014)
Oyster	Oyster spermatozoa	DNA damage	DNA strand breaks, comet assay	–	0.005 mg/L	Time of exposure, 1 h	Akcha *et al.* (2012)
Insect	*Drosophila* standard cross	Mutation	SMART	+	1 mM [0.169 mg/L]	Purity, 96% Increased frequency of small single spots (≥ 1 mM) and total spots (≥ 2 mM) $P = 0.05$	Kaya *et al.* (2000)
Insect	*Drosophila melanogaster*, high bioactivation cross	Mutation	SMART	–	10 mM [1.69 mg/L]	Purity, 96%	Kaya *et al.* (2000)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Plant systems	*Tradescantia* clone 4430 (spiderworts), staminal hair nuclei	DNA damage	DNA strand breaks, comet assay	+	0.0007 mM [0.12 µg/mL]	Glyphosate isopropylamine salt $P < 0.01$ for directly exposed nuclei (dose-dependent increase) and plants	Alvarez-Moya *et al.* (2011)
Plant systems	*Allium cepa* (onion)	Chromosomal damage	Chromosomal aberrations	+	3%	Single dose tested only Partial but significant reversal with distilled water	Bolognesi *et al.* (2013)
Plant systems	*Allium cepa* (onion)	Chromosomal damage	Chromosomal aberrations	–	2.88 µg/mL	Glyphosate isopropylamine	Rank *et al.* (1993)
Plant systems	*Trigonella foenum-graecum* L. (fenugreek)	Chromosomal damage	Chromosomal aberrations	+	0.2%	$P < 0.001$; positive dose–response relationship	Siddiqui *et al.* (2012)
Plant systems	*Vicia faba* (bean)	Chromosomal damage	Micronucleus formation	–	1400 ppm (1400 µg/g of soil)	Tested with two types of soil, but not without soil	De Marco *et al.* (1992)
AMPA							
Fish	*Anguilla anguilla* L. (European eel)	DNA damage	DNA strand breaks, comet assay	+	0.0118 mg/L	Time of exposure, 1 and 3 days $P < 0.05$ after 1 day of exposure	Guilherme *et al.* (2014b)
Fish	*Anguilla anguilla* L. (European eel)	Chromosomal damage	Other (ENA)	+	0.0236 mg/L	$P < 0.05$ only at highest dose after 3 day exposure (not after 1 day)	Guilherme *et al.* (2014b)
Glyphosate-based formulations							
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay	+	0.058 mg/L	$P < 0.05$ Positive dose–response relationship	Guilherme *et al.* (2010)
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay improved with the DNA-lesion-specific FPG and Endo III	+	0.058 mg/L	Glyphosate-based formulation, 30.8% Time of exposure, 1 and 3 days With FPG, $P < 0.05$; with comet assay alone, $P < 0.05$ at 116 µg/L	Guilherme *et al.* (2012b)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Anguilla anguilla* L. (European eel), blood cells	DNA damage	DNA strand breaks, comet assay improved with the DNA-lesion-specific FPG and Endo III	+	0.116 mg/L	Single dose tested only Time of exposure, 3 days; recovery from non-specific DNA damage, but not oxidative DNA damage, 14 days after exposure $P < 0.05$	Guilherme et al. (2014a)
Fish	*Anguilla anguilla* L. (European eel), liver	DNA damage	DNA strand breaks, comet assay improved with the DNA-lesion-specific FPG and Endo III	+	0.058 mg/L	Glyphosate-based formulation, 485 g/L Time of exposure, 3 days $P < 0.05$	Marques et al. (2014, 2015)
Fish	*Prochilodus lineatus* (sábalo), erythrocytes and bronchial cells	DNA damage	DNA strand breaks, comet assay	+	10 mg/L	Single dose tested only, for 6, 24, and 96 h $P < 0.05$ for both erythrocytes and bronchial cells	Cavalcante et al. (2008)
Fish	*Prochilodus lineatus* (sábalo), erythrocytes and gill cells	DNA damage	DNA strand breaks, comet assay	+	1 mg/L	Glyphosate-based formulation, 480 g/L Time of exposure, 6, 24 and 96 h $P < 0.001$ after 24 and 96 h in erythrocytes and 24 h in gill cells	Moreno et al. (2014)
Fish	*Poecilia reticulata* (guppy) gill erythrocytes	DNA damage	DNA strand breaks, comet assay	+	2.83 µL/L [1.833mg/L]	Glyphosate, 64.8%, m/v (648 g/L) $P < 0.05$	De Souza Filho et al. (2015)
Fish	*Channa punctatus* (bloch), blood and gill cells	DNA damage	DNA strand breaks, comet assay	+	3.25 mg/L	Exposure continued for 35 days; blood and gill cells collected on day 1, 7, 14, 21, 28 and 35 $P < 0.01$, for blood and gill cells; DNA damage increased with time and concentration	Nwani et al. (2013)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Corydoras paleatus* (blue leopard corydoras, mottled corydoras and peppered catfish), blood and hepatic cells	DNA damage	DNA strand breaks, comet assay	+	0.0067 mg/L	Glyphosate, 48% (corresponding to 3.20 µg/L) Single dose tested only, for 3, 6, and 9 days $P < 0.01$, in blood and in liver cells	de Castilhos Ghisi & Cestari (2013)
Fish	*Cyprinus carpio* Linnaeus (carp), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	2 mg/L (10% LC_{50}, 96 h)	Glyphosate, equivalent to 360 g/L Single dose tested only, for 16 days $P < 0.01$	Gholami-Seyedkolaei, et al. (2013)
Fish	*Carassius auratus* (goldfish), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	5 ppm	Glyphosate equivalent to 360 g/L Time of exposure, 2, 4 and 6 days After 48 h: $P < 0.05$ (5 mg/L) and $P < 0.001$ (10 and 15 mg/L)	Cavas & Könen (2007)
Fish	*Prochilodus lineatus* (sábalo) erythrocytes	Chromosomal damage	Micronucleus formation	–	10 mg/L	Single dose tested only, for 6, 24, and 96 h Nuclear abnormalities (lobed nuclei, segmented nuclei and kidney-shaped nuclei)	Cavalcante et al. (2008)
Fish	*Corydoras paleatus* (blue leopard corydoras, mottled corydoras and peppered catfish), blood and hepatic cells	Chromosomal damage	Micronucleus formation	–	0.0067 mg/L	Glyphosate, 48% (corresponding to 3.20 µg/L) Single dose tested only, for 3, 6 and 9 days	de Castilhos Ghisi & Cestari (2013)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Tilapia rendalli* (redbreast tilapia) blood erythrocytes	Chromosomal damage	Micronucleus formation	+	42 mg/kg bw	Glyphosate, 480 g/L Increased frequency of micronucleus formation vs control ($P < 0.05$) in blood samples collected 4 days after a single intra-abdominal injection of 42, 85, or 170 mg/kg bw	Grisolia (2002)
Fish	*Carassius auratus* (goldfish), erythrocytes	Chromosomal damage	Micronucleus formation	+	5 ppm	Glyphosate equivalent to 360 g/L Time of exposure, 2, 4 and 6 days Statistically significant differences: 96 h ($P < 0.05$); 144 h ($P < 0.01$)	Cavas & Könen (2007)
Fish	*Poecilia reticulata* (guppy) gill erythrocytes	Chromosomal damage	Micronucleus formation, ENA	+	1.41 µL/L [0.914 mg/L]	Glyphosate, 64.8%, m/v (648 g/L) Micronucleus formation, $P < 0.01$ Other nuclear abnormalities, $P < 0.05$ at 1.41 to 5.65 µL/L; concentration-dependent ($r^2 = 0.99$)	De Souza Filho *et al.* (2013)
Fish	*Cnesterodon decemmaculatus* (Jenyns, 1842) peripheral blood erythrocytes	Chromosomal damage	Micronucleus formation	+	3.9 mg/L	Glyphosate, 48% Time of exposure, 48 and 96 h $P < 0.05$, with 3.9 and 7.8 mg/L for 48 and 96 h	Vera-Candioti *et al.* (2013)
Fish	*Cnesterodon decemmaculatus* (Jenyns, 1842) peripheral blood erythrocytes	Chromosomal damage	Micronucleus formation	+	22.9 mg/L	Glyphosate, 48% Time of exposure, 48 and 96 h $P < 0.01$, with 22.9 and 45.9 mg/L, and $P < 0.05$ at 68.8 mg/L, for 96 h	Vera-Candioti *et al.* (2013)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Fish	*Prochilodus lineatus* (sábalo) erythrocytes	Chromosomal damage	Chromosomal aberrations	–	10 mg/L	Single dose tested only, for 6, 24, and 96 h Nuclear abnormalities (lobed nuclei, segmented nuclei and kidney-shaped nuclei)	Cavalcante *et al.* (2008)
Fish	*Anguilla anguilla* L. (European eel), peripheral mature erythrocytes	Chromosomal damage	Other (ENA)	+	0.058 mg/L	Time of exposure, 1 and 3 days Chromosomal breakage and/or chromosomal segregational abnormalities after 3 days of exposure, $P < 0.05$	Guilherme *et al.* (2010)
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	0.500 mg/egg	Glyphosate, 66.2% In-ovo exposure, blood sampling at the time of hatching $P < 0.05$ in both experiments (50–1000 µg/egg in experiment 1; 500–1750 µg/egg in experiment 2)	Poletta *et al.* (2009)
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	DNA damage	DNA strand breaks, comet assay	–	19.800 mg/L	Glyphosate, 66.2% Single dose tested only; in-ovo exposure First spraying exposure at the beginning of incubation period, a second exposure on day 35, then incubation until hatching	Poletta *et al.* (2011)
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	Chromosomal damage	Micronucleus formation	+	0.500 mg/egg	Glyphosate, 66.2% In-ovo exposure, blood sampling at the time of hatching $P < 0.05$ in both experiments (50–1000 µg/egg in experiment 1; 500–1750 µg/egg in experiment 2)	Poletta *et al.* (2009)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Caiman	*Caiman latirostris* (broad-snouted caiman), erythrocytes	Chromosomal damage	Micronucleus fomation	+	19.8 g/L	Glyphosate, 66.2% One dose tested; in-ovo exposure First spraying exposure at the beginning of incubation period, a second exposure on day 35, then incubation until hatching. Micronucleus formation, $P < 0.001$ Damage index, $P < 0.001$	Poletta *et al.* (2011)
Frog tadpole	*Rana catesbeiana* (ouaouaron), blood	DNA damage	DNA strand breaks, comet assay	+	1.687 mg/L, p.o.	Time of exposure, 24 h $P < 0.05$, with 6.75 mg/L; and $P < 0.001$ with 27 mg/L (with 108 mg/L, all died within 24 h)	Clements *et al.* (1997)
Frog	*Eleutherodactylus johnstonei* (Antilles coqui), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	0.5 µg a.e./cm^2	Glyphosate-based formulation, 480 g/L Exposure to an homogenate mist in a 300 cm^2 glass terrarium Time of exposure: 0.5, 1, 2, 4, 8 and 24 h $P < 0.05$	Mieza-Joya *et al.* (2013)
Frog	*Euflictis cyanophlyctis* (Indian skittering frog), erythrocytes	Chromosomal damage	Micronucleus formation	+	1 mg a.e./L	Glyphosate isopropylamine salt, 41% Time of exposure: 24, 48, 72, and 96 h $P < 0.001$ at 24, 48, 72 and 96 h	Yadav *et al.* (2013)
Snail	*Biomphalaria alexandrina*, haemolymph	DNA damage	DNA strand breaks, comet assay	+	10 mg/L	Glyphosate, 48% Single dose tested only, for 24 h. The percentage of damaged DNA was 21% vs 4% (control) No statistical analysis	Mohamed (2011)
Oyster	Oysters, spermatozoa	DNA damage	DNA strand breaks, comet assay	–	5 µg/L	Glyphosate, 200 µg equivalent/L Time of exposure, 1 h	Akcha *et al.* (2012)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Clam	*Corbicula fluminea* (Asian clam) haemocytes	DNA damage	DNA strand breaks, comet assay	–	10 mg/L	Time of exposure, 96 h Significant increase when atrazine (2 or 10 mg/L) was added to glyphosate ($P < 0.05$) No increase after exposure to atrazine or glyphosate separately	dos Santos & Martinez (2014)
Mussels	*Utterbackia imbecillis* (Bivalvia: Unionidae) glochidia mussels (larvae)	DNA damage	DNA strand breaks, comet assay	–	5 mg/L	Glyphosate, 18% Doses tested: 2.5 and 5 mg/L for 24 h NOEC, 10.04 mg/L	Conners & Black (2004)
Worm	Earthworm, *Eisenia andrei*, coelomocytes	DNA damage	DNA strand breaks, comet assay	–	240 µg a.e./cm^2	Monoammonium salt, 85.4%, a.e. Epidermic exposure during 72 h (on filter paper)	Piola *et al.* (2013)
Worm	Earthworm, *Eisenia andrei*, coelomocytes	DNA damage	DNA strand breaks, comet assay	+	15 µg a.e./cm^2	Monoammonium salt, 72%, a.e. Epidermic exposure during 72 h (on filter paper) $P < 0.001$	Piola *et al.* (2013)
Worm	Earthworm, *Pheretima peguana*, coelomocytes	DNA damage	DNA strand breaks, comet assay	–	251.50 µg/cm^2	Active ingredient, 36% (w/v) Epidermic exposure 48 h on filter paper; LC_{50}, 251.50 µg/cm^2	Muangphra *et al.* (2014)
Worm	Earthworm, *Pheretima peguana*, coelomocytes	Chromosomal damage	Micronucleus formation	+	251.50 µg/cm^2	Active ingredient, 36% (w/v) Exposure, 48 h on filter paper; LC_{50}, 251.50 µg/cm^2 filter paper $P < 0.05$, for total micro-, bi-, and trinuclei frequencies at 0.25 µg/cm^2; when analysed separately, micro- and trinuclei frequencies significantly differed from controls only at the LC_{50}	Muangphra *et al.* (2014)

Table 4.5 (continued)

Phylogenetic class	Species, strain, tissue	End-point	Test	Results[a]	Dose (LED or HID)	Comments	Reference
Insect	*Drosophila melanogaster*	Mutation	Sex-linked recessive lethal mutations	+	1 ppm	Single dose tested only $P < 0.001$	Kale et al. (1995)
Plant systems	*Allium cepa* (onion)	Chromosomal damage	Chromosomal aberrations	+	1.44 µg/mL	Glyphosate-based formulation, 480 g/L. The doses of formulation were calculated as glyphosate isopropylamine $P < 0.005$	Ranalli et al. (1993)
Plant systems	*Crepis capillaris* (hawksbeard)	Chromosomal damage	Chromosomal aberrations	–	0.5%	The highest dose tested (1%) was toxic	Dimitrov et al. (2006)
Plant systems	*Hordeum vulgare* L. cv. Madalin (barley roots)	Chromosomal damage	Chromosomal aberrations	(+)	360 µg/mL (0.1%)	Reported as "significant"	Truta et al. (2011)
Plant systems	*Crepis capillaris* (hawksbeard)	Chromosomal damage	Micronucleus formation	–	0.5%	The highest dose tested (1%) was toxic	Dimitrov et al. (2006)

[a] +, positive; –, negative; (+) or (–) positive/negative in a study with limited quality

a.e., acid equivalent; AMPA, aminomethyl phosphonic acid; bw, body weight; ENA, erythrocytic nuclear abnormalities; Endo III, endonuclease III; FPG, formamidopyrimidine glycosylase; h, hour; HID, highest ineffective dose; LC_{50}, median lethal dose; LED, lowest effective dose; NOEC, no-observed effect concentration; p.o., oral; SMART, somatic mutation and recombination test

Table 4.6 Genetic and related effects of glyphosate and glyphosate-based formulations on non-mammalian systems in vitro

Phylogenetic class	Test system (species; strain)	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Glyphosate								
Eukaryote Fish	*Oreochromis niloticus* (Nile tilapia), erythrocytes	DNA damage	DNA strand breaks, comet assay	+	NT	7 µM [1.2 µg/mL]	Glyphosate isopropylamine, 96% $P \leq 0.001$; positive dose–response relationship for doses ≥ 7 µM	Alvarez-Moya et al. (2014)
Prokaryote (bacteria)	*Scytonema javanicum* (cyanobacteria)	DNA damage	DNA strand breaks, FADU assay	(+)	NT	10 µM [1.7 µg/mL] (in combination with UVB)	Co-exposure to glyphosate (not tested alone, single dose tested only) enhanced UVB-induced increases	Wang et al. (2012)
Prokaryote (bacteria)	*Anabaena spherica* (cyanobacteria)	DNA damage	DNA strand breaks, FADU assay	(+)	NT	10 µM [1.7 µg/mL] (in combination with UVB)	Co-exposure to glyphosate (not tested alone, single dose tested only) enhanced UVB-induced increases	Chen et al. (2012)
Prokaryote (bacteria)	*Microcystis viridis* (cyanobacteria)	DNA damage	DNA strand breaks, FADU assay	(+)	NT	10 µM [1.7 µg/mL] (in combination with UVB)	Co-exposure to glyphosate (not tested alone, single dose tested only) enhanced UVB-induced increases	Chen et al. (2012)
Prokaryote (bacteria)	*Bacillus B. subtilis*	Differential toxicity	Rec assay	–	NT	2000 µg/disk		Li & Long (1988)
Prokaryote (bacteria)	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 and TA100	Mutation	Reverse mutation	–	–	5000 µg/plate		Li & Long (1988)
Prokaryote (bacteria)	*Escherichia coli* WP2	Mutation	Reverse mutation	–	–	5000 µg/plate		Li & Long (1988)

Table 4.6 (continued)

Phylogenetic class	Test system (species, strain)	End-point	Test	Results[a]		Concentration (LEC or HIC)	Comments	Reference
				Without metabolic activation	With metabolic activation			
Acellular systems	Prophage superhelical PM2 DNA	DNA damage	DNA strand breaks	(–)	NT	75 mM [12.7 mg/mL] (in combination with H_2O_2 (100 µM)	Glyphosate inhibited H_2O_2-induced damage of PM2 DNA at concentrations where synergism was observed in cellular DNA damage (data NR)	Lueken *et al.* (2004)
Glyphosate-based formulations								
Prokaryote (bacteria)	*Salmonella typhimurium* TA98	Mutation	Reverse mutation	+	–	360 µg/plate	Glyphosate isopropylammonium salt, 480 g/L	Rank *et al.* (1993)
Prokaryote (bacteria)	*Salmonella typhimirium* TA100	Mutation	Reverse mutation	–	+	720 µg/plate	Glyphosate isopropylammonium salt, 480 g/L	Rank *et al.* (1993)

[a] +, positive; –, negative; (+) or (–) positive/negative in a study with limited quality

FADU, fluorometric analysis of DNA unwinding; HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested; UVB, ultraviolet B

Additionally, although all four glyphosate-based formulations dramatically reduced the transcription of ERα and ERβ in ERE-transfected HepG2 cells, glyphosate alone had no significant effect. Glyphosate and all four formulations reduced androgen-receptor transcription in the breast cancer cell line MDA-MB453-kb2, which has a high level of androgen receptor, with the formulations showing greater activity than glyphosate alone.

In a human placental cell line derived from choriocarcinoma (JEG3 cells), 18 hours of exposure to a glyphosate-based formulation (IC_{50} = 0.04%) decreased aromatase activity (Richard *et al.*, 2005). Glyphosate alone was without effect. The concentrations used did not affect cell viability.

Glyphosate, at non-overtly toxic concentrations, decreased aromatase activity in fresh human placental microsomes and transformed human embryonic kidney cells (293) transfected with human aromatase cDNA (Benachour *et al.*, 2007). A glyphosate-based formulation, at non-overtly toxic concentrations, had the same effect. The formulation was more active at equivalent doses than glyphosate alone.

In human androgen receptor and ERα and ERβ reporter gene assays using the Chinese hamster ovary cell line (CHO-K1), glyphosate had neither agonist nor antagonist activity (Kojima *et al.*, 2004, 2010).

(ii) Non-human mammalian experimental systems

In vivo

No data were available to the Working Group.

In vitro

Benachour *et al.* (2007) and Richard *et al.* (2005) reported that glyphosate and a glyphosate-based formulation inhibited aromatase activity in microsomes derived from equine testis. Richard *et al.* (2005) reported an absorbance spectrum consistent with an interaction between a nitrogen atom of glyphosate and the active site of the purified equine aromatase enzyme.

In the mouse MA-10 Leydig cell tumour cell line, a glyphosate-based formulation (glyphosate, 180 mg/L) markedly reduced [$(Bu)_2$] cAMP-stimulated progesterone production (Walsh *et al.*, 2000). The inhibition was dose-dependent, and occurred in the absence of toxicity or parallel reductions in total protein synthesis. In companion studies, the formulation also disrupted steroidogenic acute regulatory protein expression, which is critical for steroid hormone synthesis. Glyphosate alone did not affect steroidogenesis at any dose tested up to 100 µg/L. Forgacs *et al.* (2012) found that glyphosate (300 µM) had no effect on testosterone production in a novel murine Leydig cell line (BLTK1). Glyphosate did not modulate the effect of recombinant human chorionic gonadotropin, which served as the positive control for testosterone production.

(iii) Non-mammalian experimental systems

Gonadal tissue levels of testosterone, 17β-estradiol and total microsomal protein were significantly reduced in adult snails (*Biomphalaria alexandrina*) exposed for 3 weeks to a glyphosate-based formulation (glyphosate, 48%) at the LC_{10} (10% lethal concentration) (Omran & Salama, 2013). These effects persisted after a 2-week recovery period, although the impact on 17β-estradiol was reduced in the recovery animals. The formulation also induced marked degenerative changes in the ovotestis, including absence of almost all the gametogenesis stages. CYP450 1B1, measured by enzyme-linked immunosorbent assay (ELISA), was substantially increased in the treated snails, including after the recovery period.

Glyphosate (0.11 mg/L for 7 days) did not increase plasma vittelogenin levels in juvenile rainbow trout (Xie *et al.*, 2005).

(b) Other pathways

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

Glyphosate did not exhibit agonist activity in an assay for a human pregnane X receptor (PXR) reporter gene in a CHO-K1 cell line (Kojima *et al.*, 2010).

(ii) Non-human mammalian experimental systems

In vivo

In rats, glyphosate (300 mg/kg bw, 5 days per week, for 2 weeks) had no effecton the formation of peroxisomes, or the activity of hepatic carnitine acetyltransferase and catalase, and did not cause hypolipidaemia, suggesting that glyphosate does not have peroxisome proliferator-activated receptor activity (Vainio *et al.*, 1983).

In vitro

Glyphosate was not an agonist for mouse peroxisome proliferator-activated receptors PPARα or PPARγ in reporter gene assays using CV-1monkey kidney cells in vitro (Kojima *et al.*, 2010). Glyphosate was also not an agonist for the aryl hydrocarbon receptor in mouse hepatoma Hepa1c1c7cells stably transfected with a reporter plasmid containing copies of dioxin-responsive element (Takeuchi *et al.*, 2008).

(iii) Non-mammalian experimental systems

As a follow-up to experiments in which injection of glyphosate, or incubation with a glyphosate-based formulation (glyphosate, 48%), caused chick and frog (*Xenopus laevis*) cephalic and neural crest terata characteristic of retinoic acid signalling dysfunction, Paganelli *et al.*, (2010) measured retinoic acid activity in tadpoles exposed to a glyphosate-based formulation. Retinoic activity measured by a reporter gene assay was increased by the formulation, and a retinoic acid antagonist blocked the effect.This indicated a possible significant modulation of retinoic acid activity by glyphosate.

4.2.3 Oxidative stress, inflammation,and immunosuppression

(a) Oxidative stress

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

Several studies examined the effects of glyphosate on oxidative stress parameters in the human keratinocyte cell line HaCaT. Gehin *et al.* (2005) found that a glyphosate-based formulation was cytotoxic to HaCaT cells, but that addition of antioxidants reduced cytotoxicity. Elie-Caille *et al.* (2010) showed that incubation of HaCaT cells with glyphosate at 21 mM (the half maximal inhibitory concentration for cytotoxicity, IC_{50}) for 18 hours increased production of hydrogen peroxide (H_2O_2) as shown by dichlorodihydrofluorescein diacetate assay. Similarly, George & Shukla (2013) exposed HaCaT cells to a glyphosate-based formulation (glyphosate, 41%; concentration, up to 0.1 mM) and evaluated oxidative stress using the dichlorodihydrofluorescein diacetate assay. Theformulation (0.1 mM) increased maximum oxidant levels by approximately 90% compared with vehicle, an effect similar to that of H_2O_2 (100 mM). Pre-treatment of the cells with the antioxidant *N*-acetylcysteine abrogated generation of oxidants by both the formulation and by H_2O_2. *N*-Acetylcysteine also inhibited cell proliferation induced by the glyphosate-based formulation (0.1 mM). [The Working Group noted the recog - nized limitations of using dichlorodihydrofluorescein diacetate as a marker of oxidative stress (Bonini *et al.*, 2006; Kalyanaraman *et al.*, 2012),

and that the studies that reported this end-point as the sole evidence for oxidative stress should thus be interpreted with caution.]

Chaufan *et al.* (2014) evaluated the effects of glyphosate, AMPA (the main metabolite of glyphosate), and a glyphosate-based formulation on oxidative stress in HepG2 cells. The formulation, but not glyphosate or AMPA, had adverse effects. Specifically, the formulation increased levels of reactive oxygen species, nitrotyrosine formation, superoxide dismutase activity, and glutathione, but did not have an effect on catalase or glutathione-*S*-transferase activities. Coalova *et al.* (2014) exposed Hep2 cells to a glyphosate-based formulation (glyphosate as isopropylamine salt, 48%) at the LC_{20} (concentration not otherwise specified) and evaluated various parameters of oxidative stress. Exposure to the formulation for 24 hours increased catalase activity and glutathione levels, but did not have an effect on superoxide dismutase or glutathione-*S*-transferase activity.

Using blood samples from non-smoking male donors, Mladinic *et al.* (2009b) examined the effects of in-vitro exposure to glyphosate on oxidative DNA damage in primary lymphocyte cultures and on lipid peroxidation in plasma. Both parameters were significantly elevated at glyphosate concentrations of 580 µg/mL (~3.4 mM), but not at lower concentrations. Kwiatkowska *et al.* (2014) examined the effects of glyphosate, its metabolite AMPA, and *N*-methylglyphosate (among other related compounds) in human erythrocytes isolated from healthy donors. The erythrocytes were exposed at concentrations of 0.01–5 mM for 1, 4, or 24 hours before flow cytometric measurement of the production of reactive oxygen species with dihydrorhodamine 123. Production of reactive oxygen species was increased by glyphosate (≥ 0.25 mM), AMPA (≥ 0.25mM), and *N*-methylglyphosate (≥ 0.5mM).

(ii) Non-human mammalian experimental systems

Most of the studies of oxidative stress and glyphosate were conducted in rats and mice, and examined a range of exposure durations, doses, preparations (glyphosate and glyphosate-based formulations), administration routes and tissues. In addition, various end-points were evaluated to determine whether oxidative stress is induced by exposure to glyphosate. Specifically, it was found that glyphosate induces production of free radicals and oxidative stress in mouse and rat tissues through alteration of antioxidant enzyme activity, depletion of glutathione, and increases in lipid peroxidation. Increases in biomarkers of oxidative stress upon exposure to glyphosate in vivo have been observed in blood plasma (Astiz *et al.*, 2009b), liver (Bolognesi *et al.*, 1997; Astiz *et al.*, 2009b), skin (George *et al.*, 2010), kidney (Bolognesi *et al.*, 1997; Astiz *et al.*, 2009b), and brain (Astiz *et al.*, 2009b). Several studies demonstrated similar effects with a glyphosate-based formulation in the liver (Bolognesi *et al.*, 1997; Cavuşoğlu *et al.*, 2011; Jasper *et al.*, 2012), kidney (Bolognesi *et al.*, 1997; Cavuşoğlu *et al.*, 2011) and brain (Cattani *et al.*, 2014), or with a pesticide mixture containing glyphosate in the testes (Astiz *et al.*, 2013). Pre-treatment with antioxidants has been shown to mitigate the induction of oxidative stress by a glyphosate-based formulation (Cavuşoğlu *et al.*, 2011) and by a pesticide mixture containing glyphosate (Astiz *et al.*, 2013).

DNA damage associated with oxidative stress after exposure to glyphosate (e.g. as reported in Bolognesi *et al.*, 1997) is reviewed in Section 4.2.1.

(iii) Non-mammalian experimental systems

Positive associations between exposure to glyphosate and oxidative stress were reported in various tissues in aquatic organisms (reviewed in Slaninova *et al.*, 2009). Glyphosate and various glyphosate-based formulations have been tested in various fish species for effects on a plethora of end-points (e.g. lipid peroxidation, DNA

damage, expression of antioxidant enzymes, levels of glutathione), consistently presenting evidence that glyphosate can cause oxidative stress in fish(Lushchak *et al.*, 2009; Ferreira *et al.*, 2010; Guilherme *et al.*, 2010, 2012a, b, 2014a, b; Modesto & Martinez, 2010a, b; Cattaneo *et al.*, 2011; Glusczak *et al.*, 2011; de Menezes *et al.*, 2011; Ortiz-Ordoñez *et al.*, 2011; Nwani *et al.*, 2013; Marques *et al.*, 2014, 2015; Sinhorin *et al.*, 2014; Uren Webster *et al.*, 2014). Similar effects were observed in bullfrog tadpoles exposed to a glyphosate-based formulation (Costa *et al.*, 2008), and in the Pacific oyster exposed to a pesticide mixture containing glyphosate (Geret *et al.*, 2013).

(b) Inflammation and immunomodulation

(i) Humans

Studies in exposed humans

No data were available to the Working Group.

Human cells in vitro

Nakashima *et al.* (2002) investigated the effects of glyphosate on cytokine production in human peripheral blood mononuclear cells. Glyphosate (1 mM) had a slight inhibitory effect on cell proliferation, and modestly inhibited the production of IFN-gamma and IL-2. The production of TNF-α and IL-1 β was not affected by glyphosate at concentrations that significantly inhibited proliferative activity and T-cell-derived cytokine production.

(ii) Non-human mammalian experimental systems

Kumar *et al.* (2014) studied the pro-inflammatory effects of glyphosate and farm air samples in wildtype C57BL/6 and TLR4$^{-/-}$ mice, evaluating cellular response, humoral response, and lung function. In the bronchoalveolar lavage fluid and lung digests, airway exposure to glyphosate (1 or 100 µg) significantly increased the total cell count, eosinophils, neutrophils, and IgG1 and IgG2a levels. Airway exposure to glyphosate (100 ng, 1 µg, or 100 µg per day for 7 days) also produced substantial pulmonary inflammation, confirmed by histological examination. In addition, glyphosate-rich farm-air samples significantly increased circulating levels of IL-5, IL-10, IL-13 and IL-4 in wildtype and in TLR4$^{-/-}$ mice. Glyphosate was also tested in wildtype mice and significantly increased levels of IL-5, IL-10, IL-13, and IFN-γ (but not IL-4). The glyphosate-induced pro-inflammatory effects were similar to those induced by ovalbumin, and there were no additional or synergistic effects when ovalbumin was co-administered with glyphosate.

Pathological effects of glyphosate on the immune system have been reported in 13-week rat and mouse feeding studies by the NTP (Chan & Mahler, 1992). Relative thymus weight was decreased in male rats exposed for 13 weeks, but increased in male mice. Treatment-related changes in haematological parameters were observed in male rats at 13 weeks and included mild increases in haematocrit [erythrocyte volume fraction] and erythrocytes at 12 500, 25 000, and 50 000 ppm, haemoglobin at 25 000 and 50 000 ppm, and platelets at 50 000 ppm. In female rats, small but significant increases occurred in lymphocyte and platelet counts, leukocytes, mean corpuscular haemoglobin, and mean corpuscular volume at 13 weeks.

Blakley (1997) studied the humoral immune response in female CD-1 mice given drinking-water containing a glyphosate-based formulation at concentrations up to 1.05% for 26 days. The mice were inoculated with sheep erythrocytes to produce a T-lymphocyte, macrophage-dependent antibody response on day 21 of exposure. Antibody production was not affected by the formulation.

(iii) Non-mammalian experimental systems

A positive association between exposure to glyphosate and immunotoxicity in fish has been reported. Kreutz *et al.* (2011) reported alterations

in haematological and immune-system parameters in silver catfish (*Rhamdia quelen*) exposed to sublethal concentrations (10% of the median lethal dose, LC_{50}, at 96 hours) of a glyphosate-based herbicide. Numbers of blood erythrocytes, thrombocytes, lymphocytes, and total leukocytes were significantly reduced after 96 hours of exposure, while the number of immature circulating cells was increased. The phagocytic index, serum bacteria agglutination, and total peroxidase activity were significantly reduced after 24 hours of exposure. Significant decreases in serum bacteria agglutination and lysozyme activity were found after 10 days of exposure. No effect on serum bactericidal and complement natural haemolytic activity was seen after 24 hours or 10 days of exposure to glyphosate.

el-Gendy *et al.* (1998) demonstrated effects of a glyphosate-based formulation (glyphosate, 48%) at 1/1000 of the concentration recommended for field application on humoral and cellular immune response in bolti fish (*Tilapia nilotica*). The mitogenic responses of splenocytes to phytohaemagglutinin, concanavalin A, and lipopolysaccharide in fish exposed to glyphosate for 96 hours were gradually decreased and reached maximum depression after 4 weeks. Glyphosate also produced a concentration-dependent suppression of in-vitro plaque-forming cells in response to sheep erythrocytes.

4.2.4 Cell proliferation and death

(a) Humans

(i) Studies in exposed humans

No data were available to the Working Group.

(ii) Human cells in vitro

Cell proliferation potential was explored in HaCaT keratinocytes exposed to a glyphosate-based formulation (glyphosate, 41%; concentration, up to 0.1 mM) (George & Shukla, 2013). The formulation increased the number of viable cells, as assessed by the MTT assay (based on reduction of the dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) at concentrations up to 0.1 mM, while concentration- and incubation-time-dependent reductions were seen at higher concentrations (up to 1 mM). The formulation (0.01 or 0.1 mM for 72 hours) significantly enhanced cell proliferation (measured by staining for either proliferating cell nuclear antigen or 5-bromo-2′-deoxyuridine); at 0.1 mM, the increases exceeded levels for the positive control, tetradecanoyl-phorbol-13-acetate. The proportion of S-phase cells (assessed using flow cytometry) and the expression of G1/S cell-cycle regulatory proteins (cyclins D1 and E, CDK2, CDK4, and CDK6) increased after exposure to the formulation or the positive control.

Li *et al.* (2013) reported that glyphosate and AMPA inhibited cell growth in eight human cancer cell lines, but not in two immortalized normal prostate cell lines. An ovarian (OVCAR-3) and a prostate (C4–2B) cell line showed the greatest loss in viability, with glyphosate or AMPA at 15–50 mM. Further assays were conducted on AMPA, but not glyphosate, in two prostate cancer cell lines (C4–2B and PC-3), and found cell-cycle arrest (decreased entry of cells into S-phase) and increased apoptosis. [The Working Group noted that the findings from these assays with AMPA are of unclear relevance to the effects of glyphosate.]

Glyphosate (10^{-6} to 1 µM) increased growth by 15–30% relative to controls in hormone-dependent T47D breast cancer cells, but only when endogenous estrogen was minimized in the culture medium (by substitution with 10% dextran-charcoal treated fetal bovine serum). Glyphosate did not affect the growth of hormone-independent MDA-MB231 breast cancer cells cultured in either medium (Thongprakaisang *et al.*, 2013).

Glyphosate (up to 30 µM) did not show cell proliferation potential (5-bromo-2′-deoxyuridine) and did not activate caspase 3 or TP53 in human neuroprogenitor ReN CX cells (Culbreth *et al.*, 2012).

Several studies evaluated the impact of glyphosate or glyphosate-based formulations on apoptotic cell death in the HepG2 human hepatoma cell line. Glyphosate-based formulations induced apoptosis in HepG2 cells, while glyphosate alone was generally without effect or showed effects at considerably higher concentrations (Gasnier *et al.*, 2009, 2010; Mesnage *et al.*, 2013; Chaufan *et al.*, 2014; Coalova *et al.*, 2014). For example, 23.5% of the nuclei of HepG2 cells exposed to a glyphosate-based formulation showed condensed and fragmented chromatin ($P < 0.01$), and caspases 3 and 7 were significantly activated, both effects being indicative of apoptosis (Chaufan *et al.*, 2014). Caspases were unaffected by glyphosate or AMPA alone. Glyphosate and AMPA did not affect cell viability at concentrations up to 1000 mg/L, a concentration that increased rather than decreased cell viability after 48 and 72 hours of incubation. In contrast, cells exposed to glyphosate-based formulation at lower concentrations were not viable. Similarly, Coalova *et al.* (2014) reported that a glyphosate-based formulation (glyphosate, 48%) induced apoptotic cell death in HepG2 cells. Apoptosis was indicated by activation of caspases 3 and 7, and the significant fraction (17.7%) of nuclei with condensed and fragmented chromatin ($P < 0.001$).

In studies with glyphosate and nine different glyphosate-based formulations in three cell lines, glyphosate alone did not increase the activity of adenylate kinase (Mesnage *et al.*, 2013). The activity of caspases 3 and 7 was significantly increased by glyphosate in HepG2 and embryonic kidney HEK293 cells, and elevated (although not significantly) about 1.8 times above control levels in placental choriocarcinoma JEG-3 cells. Two formulations containing an ethoxylated adjuvant induced adenylate kinase activity to a greater extent than caspase activity. All formulations were reported to be more cytotoxic than glyphosate. [In concentration–response curves, glyphosate showed an effect on mitochondrial succinate dehydrogenase activity, a measure of cell viability, that was similar to that shown by one formulation. The calculated 50% lethal concentration in JEG3 cells for mitochondrial succinate dehydrogenase activity was greater for three formulations, although the values appeared inconsistent with the concentration–response curves.]

In HUVEC primary neonate umbilical cord vein cells, and 293 embryonic kidney and JEG3 placental cell lines, Benachour & Séralini (2009) found that glyphosate at relatively high concentrations induced apoptosis, as indicated by induction of caspases 3 and 7, and DNA staining and microscopy. At comparable or lower concentrations, four glyphosate-based formulations all caused primarily necrotic cell death. The umbilical cord HUVEC cells were the most sensitive (by about 100-fold) to the apoptotic effects of glyphosate.

Heu *et al.* (2012) evaluated apoptosis in immortalized human keratinocytes (HaCaT) exposed to glyphosate (5–70 mM). Based on annexin V, propidium iodide and mitochondrial staining, exposures leading to 15% cytotoxicity gave evidence of early apoptosis, while increases in late apoptosis and necrosis were observed at higher levels of cytotoxicity.

(b) Non-human mammalian experimental systems

(i) In vivo

In male Wistar rats, glyphosate (10 mg/kg bw, injected intraperitoneally three times per week for 5 weeks) reduced, but not significantly, the inner mitochondrial membrane integrity of the substantia nigra and cerebral cortex (Astiz *et al.* 2009a). Caspase 3 activity was unaltered in these tissues. Mitochondrial cardiolipin content was significantly reduced, particularly in the substantia nigra, where calpain activity was substantially higher. Glyphosate induced DNA fragmentation in the brain and liver.

(ii) In vitro

In adult Sprague Dawley rat testicular cells exposed in vitro, glyphosate (up to 1%; for 24 or 48 hours) did not provoke cell-membrane alterations (Clair *et al.*, 2012). However, caspase 3 and 7 activity increased with exposure in Sertoli cells alone, and in Sertoli and germ cell mixtures. On the other hand, a glyphosate-based formulation (a 0.1% solution, containing 0.36 g/L of glyphosate) induced membrane alterations and decreased the activity of caspase 3 and 7 in Leydig cells, and in Sertoli and germ cell mixtures. In a separate study, glyphosate increased apoptosis in primary Sertoli cell cultures from mice (Zhao *et al.*, 2013).

Glyphosate (5–40 mM, for 12, 24, 48, or 72 hours) significantly increased cell death in a time- and concentration-dependent manner in differentiated rat pheochromocytoma PC12 (neuronal) cells Gui *et al.* (2012). Apoptotic changes included cell shrinkage, DNA fragmentation, decreased Bcl2 expression, and increased Bax expression. Both autophagy and apoptosis were implicated, as pre-treatment with the pan-caspase inhibitor Z-VAD or the autophagy inhibitor 3-MA inhibited cell loss.

Induction of apoptosis by glyphosate or glyphosate-based formulations was also studied in other cell lines. Glyphosate (10 µM) induced apoptosis in rat heart H9c2 cells, the effect being enhanced when glyphosate was given in combination with the adjuvant TN-20 (5 µM), (Kim *et al.*, 2013). A glyphosate-based formulation induced apoptosis in mouse 3T3-L1 fibroblasts, and inhibited their transformation to adipocytes (Martini *et al.*, 2012). A glyphosate-based formulation (10 mM) did not increase rat hepatoma HTC cell death, but did affect mitochondrial membrane potential (Malatesta *et al.*, 2008).

Glyphosate (up to 30 µM) did not activate caspase 3 or show cell proliferation potential (5-bromo-2′-deoxyuridine) in a mouse neuroprogenitor cell line, but did activate Tp53 at the highest concentration tested (Culbreth *et al.*, 2012).

4.2.5 Other mechanisms

No data on immortalization, epigenetic alterations, altered DNA repair, or genomic instability after exposure to glyphosate were available to the Working Group.

4.3 Data relevant to comparisons across agents and end-points

No data on high-throughput screening or other relevant data were available to the Working Group. Glyphosate was not tested by the Tox21 and ToxCast research programmes of the government of the USA (Kavlock *et al.* 2012; Tice *et al.*, 2013).

4.4 Cancer susceptibility data

No studies that examined genetic, life-stage, or other susceptibility factors with respect to adverse health outcomes that could be associated with exposure to glyphosate were identified by the Working Group.

4.5 Other adverse effects

4.5.1 Humans

In the USA in the past decade, poison-control centres have reported more than 4000 exposures to glyphosate-containing herbicides, of which several hundred were evaluated in a health-care facility, and fatalities were rare (Rumack, 2015). In a pesticide surveillance study carried out by the National Poisons Information Service of the United Kingdom, glyphosate was among the most common pesticide exposure implicated in severe or fatal poisoning cases between 2004 and 2013 (Perry *et al.*, 2014). Deliberate poisonings with glyphosate resulting in toxicity and fatality

have been reported in many countries, including Australia (Stella & Ryan, 2004), Denmark (Mortensen *et al.*, 2000), India (Mahendrakar *et al.*, 2014), Japan (Motojyuku *et al.*, 2008), Republic of Korea (Park *et al.*, 2013), New Zealand (Temple & Smith, 1992), Sri Lanka (Roberts *et al.*, 2010), Taiwan, China (Chen *et al.*, 2009), and Thailand (Sribanditmongkol *et al.*, 2012).

Glyphosate demonstrated no potential for photo-irritation or photo-sensitization in 346 volunteers exposed dermally on normal or abraded skin (Hayes & Laws, 1991). On the other hand, Mariager *et al.* (2013) reported severe burns after prolonged accidental dermal exposure to a glyphosate-based formulation.

4.5.2 Experimental systems

Glyphosate was tested in nine regulatory submissions included in the Toxicity Reference Database (ToxRefDB) and reviewed by the EPA (EPA, 2015). Specifically, study design, treatment group, and treatment-related effect information were captured for four long-term studies and/or carcinogenicity studies, one short-term study, two multigeneration studies of reproductivity, and two studies of developmental toxicity. The NTP also tested glyphosate in a 13-week study in rats and mice (Chan & Mahler, 1992).

In a long-term combined study of toxicity and carcinogenicity in rats given glyphosate at nominal doses of 100, 400, and 1000 mg/kg bw per day, inflammation was observed in the stomach mucosa of females at the intermediate and highest doses (EPA, 1990, 1991b). In males at the highest dose, liver weight, cataracts and lens degeneration in the eyes, and urine specific gravity were increased, while body weight, body-weight gain, and urinary pH were decreased. Pancreatic acinar cell atrophy was observed in males at the highest dose. Pancreatic inflammation was also observed in male rats at the highest dose in a short-term study (nominal doses of 50, 250, and 1000 mg/kg bw per day) (EPA, 1987). In the study by the NTP, cytoplasmic alteration was observed in the parotid and submandibular salivary glands of rats (Chan & Mahler, 1992).

In a study of carcinogenicity in mice given glyphosate at doses of 150, 1500, or 4500 mg/kg bw per day, liver hypertrophy and necrosis were observed in males at the highest dose (EPA, 1983). Other effects in males at the highest dose included increased testes weight, interstitial nephritis, and decreased body weight. In females at the highest dose, ovary weights were increased, proximal tubule epithelial basophilia and hypertrophy was observed, and body weights were decreased. In the study by the NTP, cytoplasmic alteration was observed in the parotid salivary glands in mice (Chan & Mahler, 1992).

Developmental and reproductive toxicity

In a study of developmental toxicity in rats given glyphosate at a dose of 300, 1000, or 3500 mg/kg bw per day, reduced implantation rates and fewer live fetuses were observed in dams at the highest dose (EPA, 1980b). In fetuses at the highest dose, unossified sternebra were observed and fetal weight was reduced.

5. Summary of Data Reported

5.1 Exposure data

Glyphosate is a broad-spectrum herbicide that is effective at killing or suppressing all plant types, including grasses, perennials, and woody plants. The herbicidal activity of glyphosate was discovered in 1970 and since then its use has increased to a point where it is now the most heavily used herbicide in the world, with an annual global production volume in 2012 of more than 700 000 tonnes used in more than 750 different products. Changes in farming practice and the development of genetically modified crops that are resistant to glyphosate have contributed to the increase in use.

There is little information available on occupational or community exposure to glyphosate. Glyphosate can be found in soil, air, surface water and groundwater, as well as in food. It has been detected in air during agricultural herbicide-spraying operations. Glyphosate was detected in urine in two studies of farmers in the USA, in urban populations in Europe, and in a rural population living near areas sprayed for drug eradication in Columbia. However, urinary concentrations were mostly below the limit of detection in several earlier studies of forestry workers who sprayed glyphosate. Exposure of the general population occurs mainly through diet.

5.2 Human carcinogenicity data

In its evaluation of the epidemiological studies reporting on cancer risks associated with exposure to glyphosate, the Working Group identified seven reports from the Agricultural Health Study (AHS) cohort and several reports from case–control studies. The AHS cohort, the pooled analyses of the case–control studies in the midwest USA, and the cross-Canada study were considered key investigations because of their relatively large size. Reports from two or more independent studies were available for non-Hodgkin lymphoma (NHL), multiple myeloma, Hodgkin lymphoma, glioma, and prostate. For the other cancer sites, results from only one study were available for evaluation.

5.2.1 NHL and other haematopoietic cancers

Two large case–control studies of NHL from Canada and the USA, and two case–control studies from Sweden reported statistically significant increased risks of NHL in association with exposure to glyphosate. For the study in Canada, the association was seen among those with more than 2 days/year of exposure, but no adjustment for other pesticides was done. The other three studies reported excesses for NHL associated with exposure to glyphosate, after adjustment for other pesticides (reported odds ratio were 2.1 (95% CI, 1.1–4.0); 1.85 (95% CI, 0.55–6.2); and 1.51 (95% CI, 0.77–2.94). Subtype-specific analyses in a Swedish case–control study indicated positive associations for total NHL, as well as all subtypes, but this association was statistically significant only for the subgroup of lymphocytic lymphoma/chronic lymphocytic leukaemia (OR, 3.35; 95% CI, 1.42–7.89). An elevated risk (OR, 3.1; 95% CI, 0.6–17.1) was also found for B-cell lymphoma in an European study based on few cases. One hospital-based case–control study from France did not find an association between exposure to glyphosate and NHL (OR, 1.0; 95% CI, 0.5–2.2) based on few exposed cases.

A roughly twofold excess of multiple myeloma, a subtype of NHL, was reported in three studies: only among the highest category of glyphosate use (> 2 days/year) in the large Canadian case–control study, in a case–control study from Iowa, USA, and in a French case–control study (all not statistically significant). These three studies did not adjust for the effect of other pesticides. In the AHS, there was no association with NHL (OR, 1.1; 0.7–1.9). For multiple myeloma, relative risk was 1.1 (95% CI, 0.5–2.4) when adjusted for age only; but was 2.6 (95% CI, 0.7–9.4) when adjusted for multiple confounders. No excess in leukaemia was observed in a case–control study in Iowa and Minnesota, USA, or in the AHS.

In summary, case–control studies in the USA, Canada, and Sweden reported increased risks for NHL associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides. The AHS cohort did not show an excess of NHL. The Working Group noted that there were excesses reported for multiple myeloma in three studies; however, they did not weight this evidence as strongly as that of NHL because of the possibility that chance could not be excluded; none of the

risk estimates were statistically significant nor were they adjusted for other pesticide exposures.

5.2.2. Other cancer sites

No association of glyphosate with cancer of the brain in adults was found in the Upper Midwest Health case–control study. No associations in single case–control studies were found for cancers of the oesophagus and stomach, prostate, and soft-tissue sarcoma. For all other cancer sites (lung, oral cavity, colorectal, pancreas, kidney, bladder, breast, prostate, melanoma) investigated in the large AHS, no association with exposure to glyphosate was found.

5.3 Animal carcinogenicity data

Glyphosate was tested for carcinogenicity in male and female mice by dietary administration in two studies, and in male and female rats by dietary administration in five studies and in drinking-water in one study. A glyphosate-based formulation was also tested in drinking-water in one study in male and female rats, and by skin application in one initiation–promotion study in male mice.

There was a positive trend in the incidence of renal tubule carcinoma and of renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. Renal tubule carcinoma is a rare tumour in this strain of mice. No significant increase in tumour incidence was seen in female mice in this study. In the second feeding study, there was a significant positive trend in the incidence of haemangiosarcoma in male CD-1 mice. No significant increase in tumour incidence was seen in female mice in this study.

For the five feeding studies in rats, two studies in the Sprague-Dawley strain showed a significant increase in the incidence of pancreatic islet cell adenoma in males – one of these two studies also showed a significant positive trend in the incidences of hepatocellular adenoma in males and of thyroid C-cell adenoma in females. Two studies (one in Sprague-Dawley rats, one in Wistar rats) found no significant increase in tumour incidence at any site. One study in Wistar rats was inadequate for the evaluation because of the short duration of exposure.

In the study in Wistar rats given drinking-water containing glyphosate, there was no significant increase in tumour incidence.

A glyphosate-based formulation was found to be a skin-tumour promoter in the initiation–promotion study in male Swiss mice. The study of a glyphosate-based formulation in drinking-water in Sprague-Dawley rats was inadequate for the evaluation because of the small number of animals per group, and the limited information provided on tumour histopathology and incidence in individual animals. These studies of a chemical mixture containing glyphosate were considered inadequate to evaluate the carcinogenicity of glyphosate alone.

5.4. Other relevant data

Direct data on absorption of glyphosate in humans were not available to the Working Group. Glyphosate was detected in the urine of agricultural workers in several studies, and in the blood of poisoning cases, indicative of absorption. Some evidence for absorption through human skin (~2%) was reported in studies in vitro. The minor role of dermal absorption was also shown in a study in non-human primate model in vivo. However, no study examined the rates of absorption in humans. In rodents, several studies showed up to 40% absorption after oral administration of a single or repeated dose.

Glyphosate was measured in human blood. No data on parenchymal tissue distribution for glyphosate in humans were available to the Working Group. In rats given glyphosate by oral administration, concentrations in tissues had the following rank order: kidneys > spleen > fat > liver. Repeated administration had no effect

on the distribution of glyphosate. In a study in rats, the half-life of glyphosate in plasma was estimated to be more than 1 day, indicating that glyphosate is not rapidly eliminated.

In the environment, glyphosate is degraded by soil microbes, primarily to aminomethylphosphonic acid (AMPA) and carbon dioxide. Glyphosate is not efficiently metabolized in humans or other mammals. In rats, small amounts of AMPA were detected in the plasma and in the colon, with the latter being attributed to intestinal microbial metabolism. In humans, small amounts of AMPA are detectable in blood in cases of deliberate glyphosate poisoning. Few studies examined the possible effects of glyphosate-based formulations on metabolizing enzymes, but no firm conclusions could be drawn from these studies.

Studies in rodents showed that systemically absorbed glyphosate is excreted unchanged into the urine, and that the greatest amount is excreted in the faeces, indicating poor absorption. Glyphosate was detected in the urine of humans who were exposed occupationally to glyphosate. AMPA has also been detected in human urine.

Glyphosate is not electrophilic.

A large number of studies examined a wide range of end-points relevant to genotoxicity with glyphosate alone, glyphosate-based formulations, and AMPA.

There is strong evidence that glyphosate causes genotoxicity. The evidence base includes studies that gave largely positive results in human cells in vitro, in mammalian model systems in vivo and in vitro, and studies in other non-mammalian organisms. In-vivo studies in mammals gave generally positive results in the liver, with mixed results for the kidney and bone marrow. The end-points that have been evaluated in these studies comprise biomarkers of DNA adducts and various types of chromosomal damage. Tests in bacterial assays gave consistently negative results.

The evidence for genotoxicity caused by glyphosate-based formulations is strong. There were three studies of genotoxicity end-points in community residents exposed to glyphosate-based formulations, two of which reported positive associations. One of these studies examined chromosomal damage (micronucleus formation) in circulating blood cells before and after aerial spraying with glyphosate-based formulations and found a significant increase in micronucleus formation after exposure in three out of four different geographical areas. Additional evidence came from studies that gave largely positive results in human cells in vitro, in mammalian model systems in vivo and in vitro, and studies in other non-mammalian organisms. The end-points that were evaluated in these studies comprised biomarkers of DNA adducts and various types of chromosomal damage. The pattern of tissue specificity of genotoxicity end-points observed with glyphosate-based formulations is similar to that observed with glyphosate alone. Tests in bacterial assays gave generally negative results.

For AMPA, the evidence for genotoxicity is moderate. While the number of studies that examined the effects of AMPA was not large, all of the studies gave positive results. Specifically, genotoxicity was reported in a study in humans in vitro, a study in mammals in vivo, a study in mammals in vitro, and one study in eels in vivo.

Strong evidence exists that glyphosate, AMPA, and glyphosate-based formulations can induce oxidative stress. Evidence came from studies in many rodent tissues in vivo, and human cells in vitro. In some of these studies, the mechanism was challenged by co-administration of antioxidants and observed amelioration of the effects. Similar findings have been reported in fish and other aquatic species. Various end-points (e.g. lipid peroxidation markers, oxidative DNA adducts, dysregulation of antioxidant enzymes) have been evaluated in numerous studies. This

increased the confidence of the Working Group in the overall database.

There is weak evidence that glyphosate or glyphosate-based formulations induce receptor-mediated effects. In multiple experiments, glyphosate-based formulations affected aromatase activity; glyphosate was active in a few of these studies. Some activity in other nuclear receptor-mediated pathways has been observed for glyphosate or glyphosate-based formulations. In one series of experiments, glyphosate was not found to be a ligand to several receptors and related proteins (aryl hydrocarbon receptor, peroxisome proliferator-activated receptors, pregnane X receptor).

There is weak evidence that glyphosate may affect cell proliferation or death. Several studies in human and rodent cell lines have reported cytotoxicity and cell death, the latter attributed to the apoptosis pathway. Studies that examined the effects of glyphosate alone or a glyphosate-based formulation found that glyphosate alone had no effect, or a weaker effect than the formulation.

There is weak evidence that glyphosate may affect the immune system, both the humoral and cellular response, upon long-term treatment in rodents. Several studies in fish, with glyphosate or its formulations, also reported immunosuppressive effects.

With regard to the other key characteristics of human carcinogens (IARC, 2014), the Working Group considered that the data were too few for an evaluation to be made.

Severe or fatal human poisoning cases have been documented worldwide. In rodents, organ and systemic toxicity from exposures to glyphosate are demonstrated by liver-weight effects and necrosis in animals at high doses. Additionally, effects on the pancreas, testes, kidney and ovaries, as well as reduced implantations and unossified sternebra were seen at similar doses.

No data on cancer-related susceptibility after exposure to glyphosate were available to the Working Group.

Overall, the mechanistic data provide strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans.

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate.

6.3 Overall evaluation

Glyphosate is *probably carcinogenic to humans (Group 2A).*

6.4 Rationale

In making this overall evaluation, the Working Group noted that the mechanistic and other relevant data support the classification of glyphosate in Group 2A.

In addition to limited evidence for the carcinogenicity of glyphosate in humans and sufficient evidence for the carcinogenicity of glyphosate in experimental animals, there is strong evidence that glyphosate can operate through two key characteristics of known human carcinogens, and that these can be operative in humans. Specifically:

- There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals.

One study in several communities in individuals exposed to glyphosate-based formulations also found chromosomal damage in blood cells; in this study, markers of chromosomal damage (micronucleus formation) were significantly greater after exposure than before exposure in the same individuals.

- There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro. This mechanism has been challenged experimentally by administering antioxidants, which abrogated the effects of glyphosate on oxidative stress. Studies in aquatic species provide additional evidence for glyphosate-induced oxidative stress.

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To: Sterling, Sherry[Sterling.Sherry@epa.gov]
From: Housenger, Jack
Sent: Wed 5/20/2015 1:37:38 PM
Subject: RE: HHS

Great

thanks

From: Sterling, Sherry
Sent: Wednesday, May 20, 2015 9:35 AM
To: Housenger, Jack
Subject: FW: HHS

Jack – per Jim's request:

Patrick Breysse: 770.488.0604 and his email is pjb7@cdc.gov.

LT Jona Ogden (Special Assistant): 770-488-7374

Let me know if you need anything else.

Sherry

202-564-2701

From: Jones, Jim
Sent: Wednesday, May 20, 2015 8:36 AM
To: Sterling, Sherry
Subject: RE: HHS

Can you send his name and number to Jack? Jack will call him. Thx

From: Sterling, Sherry

Sent: Wednesday, May 20, 2015 6:36 AM
To: Jones, Jim
Subject: RE: HHS

Jim – he is Dr. Patrick Breysse. I have a general phone number, but it seems that everything there is closed until 8:00. I will keep trying….

From: Jones, Jim
Sent: Tuesday, May 19, 2015 5:50 PM
To: Sterling, Sherry
Subject: Fwd: HHS

Sherry. Can you get me the contact info for the head of NCEH at CDC. I believe that person is responsible for atsdr. Thx

Sent from my iPhone

Begin forwarded message:

> **From:** "Housenger, Jack" <Housenger.Jack@epa.gov>
> **Date:** May 19, 2015 at 4:50:11 PM EDT
> **To:** "Jones, Jim" <Jones.Jim@epa.gov>
> **Subject: RE: HHS**
>
> Yes
>
> Jess checked with them
>
> They are
>
> It is on the agenda for the general
>
> It has been difficult to get information

> **From:** Jones, Jim
> **Sent:** Tuesday, May 19, 2015 4:33 PM
> **To:** Housenger, Jack
> **Subject:** Fwd: HHS

Monsanto thinks atsdr is doing a glyphosate
Assessment. Could you guys run that down?
Sent from my iPhone

Begin forwarded message:

From: "DYKES, MICHAEL D [AG/1920]" <michael.d.dykes@monsanto.com>
Date: May 19, 2015 at 3:28:05 PM EDT
To: Jim Jones <jones.jim@epa.gov>
Subject: HHS

Jim
We discussed briefly at the Ag Committee hearing the glyphosate review by the HHS Agency that was reviewing glyphosate and you were not aware of their review. Did you learn anything more about their efforts?

Thank you
Michael

Sent from my iPhone

To: Jones, Jim[Jones.Jim@epa.gov]
From: Housenger, Jack
Sent: Tue 5/19/2015 8:50:12 PM
Subject: RE: HHS

Yes

Jess checked with them

They are

It is on the agenda for the general

It has been difficult to get information

From: Jones, Jim
Sent: Tuesday, May 19, 2015 4:33 PM
To: Housenger, Jack
Subject: Fwd: HHS

Monsanto thinks atsdr is doing a glyphosate
Assessment. Could you guys run that down?
Sent from my iPhone

Begin forwarded message:

> **From:** "DYKES, MICHAEL D [AG/1920]" <michael.d.dykes@monsanto.com>
> **Date:** May 19, 2015 at 3:28:05 PM EDT
> **To:** Jim Jones <jones.jim@epa.gov>
> **Subject: HHS**
>
> Jim
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>
> Thank you
> Michael
>
> Sent from my iPhone
> This e-mail message may contain privileged and/or confidential information, and is intended to be received only by persons entitled
> to receive such information. If you have received this e-mail in error, please notify the

To: Richard Aucoin[richard.aucoin@hc-sc.gc.ca]
From: Housenger, Jack
Sent: Fri 3/27/2015 1:50:09 PM
Subject: FW:

From: Housenger, Jack
Sent: Tuesday, March 24, 2015 12:01 PM
To: Jordan, William
Subject: FW:

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, March 24, 2015 10:24 AM
To: JENKINS, DANIEL J [AG/1920]; Goodis, Michael
Cc: Keigwin, Richard; Cyran, Carissa; Rowland, Jess; Anderson, Neil; Housenger, Jack
Subject: RE:

The German Regulators have responded. We hope that EPA would consider the following in their approach to responses:

Does Glyphosate cause cancer?

(English translation of text at http://www.bfr.bund.de/cm/343/loest-glyphosat-krebs-aus.pdf)

Communication 007/2015 BfR March 23, 2015

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At a meeting of the International Agency for Research on Cancer (IARC) of the World Health Organization in Lyon in March 2015, experts gathered to discuss glyphosate and, based on the

studies they looked at, came to a different classification, namely as a Group 2A carcinogen, or "probably" carcinogenic for humans. This Classification was published in a short report in the journal "Lancet" on March 20, 2015.

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Seventeen experts from 11 countries met at the IARC in March 2015 to weigh the carcinogenicity or potential carcinogenicity of four organophosphates and glyphosate, none of which has been classified by the competent European authorities as carcinogenic or mutagenic.

On the basis of the information at the BfR's disposal, the classification of glyphosate in the Lancet on March 20 as belonging to Group 2A (probably carcinogenic to humans) is **scientifically hard to follow and apparently based on very few studies**. The IARC decision cannot be judged definitively, however, since the final IARC Monograph, in which its decision will be backed up with more information, is not yet published.

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Furthermore, IARC advances findings from animal testing as proof of a carcinogenic effect of glyphosate. All of these findings were also considered in the glyphosate appraisals of the BfR, the EU institutions and the Joint Meeting on Pesticide Residues of the WHO and FAO, which is responsible for the appraisal of pesticide ingredients. These organizations came to the overall conclusion that glyphosate is not carcinogenic. The BfR does not know how many of the 11 long-term studies on rats and mice considered valid by the BfR were available to the IARC.

The theory advanced in one study that skin tumors could be caused by a highly concentrated, irritant formulation with the ingredient were also not regarded by the EU institutions as proof for the carcinogenic qualities of glyphosate.

Indications for a gene toxic potential of glyphosate cannot be concluded from IARC's published summary, since the review also included formulations that were not further described.

The fact that different bodies reach different conclusions from different information and interpretations of experimental data is a daily reality in risk assessment. The BfR will examine IARC'sclassification in detail once the Monograph is published.

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: JENKINS, DANIEL J [AG/1920]
Sent: Monday, March 23, 2015 10:10 AM
To: 'goodis.michael@epa.gov'
Cc: 'Keigwin, Richard'; 'Cyran, Carissa'; 'rowland.jess@epa.gov'; 'anderson.neil@epa.gov'
Subject:

Mike:

Per our phone conversation. We hope EPA will correct mistakes or absences of fact with respect to its record on glyphosate (including the 2013 statement and the AHS study) as it relates to carcinogenicity.

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http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)70134-8/abstract

http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

Thanks,

Dan Jenkins

U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

To: Jordan, William[Jordan.William@epa.gov]
From: Housenger, Jack
Sent: Tue 3/24/2015 4:01:15 PM
Subject: FW:

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, March 24, 2015 10:24 AM
To: JENKINS, DANIEL J [AG/1920]; Goodis, Michael
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From: JENKINS, DANIEL J [AG/1920]
Sent: Monday, March 23, 2015 10:10 AM
To: 'goodis.michael@epa.gov'
Cc: 'Keigwin, Richard'; 'Cyran, Carissa'; 'rowland.jess@epa.gov'; 'anderson.neil@epa.gov'
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Thanks,

Dan Jenkins
U.S. Agency Lead

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Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

To: Jones, Jim[Jones.Jim@epa.gov]
From: Housenger, Jack
Sent: Tue 3/24/2015 3:57:36 PM
Subject: FW:

fyi

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, March 24, 2015 10:24 AM
To: JENKINS, DANIEL J [AG/1920]; Goodis, Michael
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Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
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1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

To: Milbourn, Cathy[Milbourn.Cathy@epa.gov]; Ingram, Earl[Ingram.Earl@epa.gov]
From: PJ.Huffstutter@thomsonreuters.com
Sent: Mon 5/2/2016 9:00:21 PM
Subject: RE: Reuters News seeks comment on why EPA withdrew documents

Thanks – and one other thing:

Monsanto issued a statement saying that "U .S. Environmental Protection Agency (EPA) has published its official classification of glyphosate as "**Not Likely to be Carcinogenic to Humans**." (Their bold and underline – not mine.)

Is this report the official classification by the EPA?

Best,

PJ

From: Milbourn, Cathy [mailto:Milbourn.Cathy@epa.gov]
Sent: Monday, May 02, 2016 3:32 PM
To: Huffstutter, PJ (Reuters News); Ingram, Earl
Subject: RE: Reuters News seeks comment on why EPA withdrew documents

PJ --will be in touch soon.

Catherine C. Milbourn

U.S. EPA HQ

Office of the Administrator

Office of Media Relations

202-564-7849 (office)

202-420-8648 (mobile)

Milbourn.cathy@epa.gov

From: PJ.Huffstutter@thomsonreuters.com [mailto:PJ.Huffstutter@thomsonreuters.com]
Sent: Monday, May 02, 2016 4:28 PM
To: Ingram, Earl <Ingram.Earl@epa.gov>
Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: Reuters News seeks comment on why EPA withdrew documents

Hi Cathy and Earl,

I'm trying to get a comment from EPA as to why the agency, per Mr. Ingram's direction, withdrew the 14 documents the agency had uploaded on Friday to the Glyphosate Registration Review's open docket folder.

So, three questions:

- Why were the documents uploaded on Friday?
- Why were they taken down on Monday afternoon?
- When is the agency expecting to complete its assessment of glyphosate?

I'm working on a tight deadline, so I appreciate any response the agency might have on this.

Thank you for your consideration and all best,

PJ Huffstutter

P.J. Huffstutter

Journalist | Thomson Reuters

Agriculture and Ag-Economy

311 S. Wacker Drive

#1200

Chicago, IL 60606

+1 312-408-8737 (work)

+1 312-730-2200 (cell)

Follow me on Twitter: @pjhuffstutter1<http://twitter.com/pjhuffstutter1>

To: Ingram, Earl[Ingram.Earl@epa.gov]
From: Nguyen, Khue
Sent: Mon 5/2/2016 7:41:37 PM
Subject: FW: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

The press inquiry came in from Bloomberg news.

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: Han, Kaythi
Sent: Monday, May 02, 2016 2:50 PM
To: Nguyen, Khue <Nguyen.Khue@epa.gov>; Britton, Wade <Britton.Wade@epa.gov>
Cc: Overbey, Dian <Overbey.Dian@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

From: Nguyen, Khue
Sent: Monday, May 02, 2016 2:43 PM
To: Han, Kaythi <Han.Kaythi@epa.gov>; Britton, Wade <Britton.Wade@epa.gov>
Cc: Overbey, Dian <Overbey.Dian@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Guys,

Ex. 5 - Deliberative Process

Thanks,

Khue Nguyen

Chemical Review Manager

Risk Management and Implementation Branch 1

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

703-347-0248

Nguyen.khue@epa.gov

From: Han, Kaythi
Sent: Monday, May 02, 2016 2:31 PM
To: Britton, Wade <Britton.Wade@epa.gov>
Cc: Overbey, Dian <Overbey.Dian@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Nguyen, Khue <Nguyen.Khue@epa.gov>
Subject: FW: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS
Importance: High

Hi Wade,

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Thanks,
Kaythi

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 2:13 PM
To: Han, Kaythi <Han.Kaythi@epa.gov>
Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Thanks Kathi I have several reporters telling me that additional documents were posted regs.gov on Friday. I'm told one was the cancer risk assessment, the CARC (this is EPA's committee?) in response to IARC. Also, the CARC report is dated Oct. 1, but it was just posted on Friday. Why the delay? Also, are there other documents to be posted in regs.gov on glyphosate? Here is the document I was referring to:
https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0361-0057

Ex. 5 - Deliberative Process

So the Bloomberg reporter is asking about this (CARC) and not IARC. Could you please send me the recent report of the CARC review about glyphosate?

What you sent is the report, as far as I can tell:

https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0361-0057

Also, why is glyphosate not listed in the Registration Review Schedules | Reevaluation: Review of Registered Pesticides | US EPA ?

Ex. 5 - Deliberative Process

Catherine C. Milbourn

U.S. EPA HQ

Office of the Administrator

Office of Media Relations

202-564-7849 (office)

202-420-8648 (mobile)

Milbourn.cathy@epa.gov

From: Han, Kaythi
Sent: Monday, May 02, 2016 1:39 PM
To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Hi Cathy,

The reporter can find the PDF of the IARC report at:
http://monographs.iarc.fr/ENG/Monographs/vol112/

Kaythi

From: Strauss, Linda
Sent: Monday, May 02, 2016 1:33 PM
To: Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Can you all let Cathy know? Thanks.

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 1:28 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: FW: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Hi Linda, I'm presuming that the IARC review is in the docket?

Good afternoon,

I am a legal reporter at Bloomberg who has a story out about a lawsuit filed against Quaker Oats containing trace levels of glyphosate. Could you please send me the recent report of the CARC review about glyphosate?

Thanks,

Rebecca

To: Jones, Jim[Jones.Jim@epa.gov]
From: Carleton, Ron
Sent: Wed 3/18/2015 1:55:35 PM
Subject: FW: Time to talk

Jim, FYI below. I'm sure you're aware of it, but wanted to pass it on.

Ron

-----Original Message-----
From: DYKES, MICHAEL D [AG/1920] [mailto:michael.d.dykes@monsanto.com]
Sent: Monday, March 16, 2015 7:19 PM
To: Carleton, Ron
Subject: RE: Time to talk

Ron
Thank you for taking my call this morning. The group I mentioned to you this morning was WHO-International Agency for Research on Cancer. They recently reviewed glyphosate and some other chemical pesticides which will be publicly released following an embargo. I wanted to alert you to this in case you received questions on this. I have also attached two US EPA documents regarding EPA's conclusion that glyphosate does not pose a cancer risk to humans.

2009 EPA Glyphosate Reg Review
Carcinogenicity was not identified as a concern in the work plan
http://www.epa.gov/oppsrrd1/registration_review/glyphosate/

2013 Federal Register Notice (FR 25396 Vol. 78, No. 84, Wednesday, May 1, 2013) Final Rule new tolerances in or on multiple commodities: "EPA has concluded that glyphosate does not pose a cancer risk to humans." http://www.gpo.gov/fdsys/pkg/FR-2013-05-01/pdf/2013-10316.pdf

Please let me know if you have additional questions on this issue.

Thank you
Michael

-----Original Message-----
From: Carleton, Ron [mailto:Carleton.Ron@epa.gov]
Sent: Monday, March 16, 2015 9:07 AM
To: DYKES, MICHAEL D [AG/1920]
Subject: Re: Time to talk

Any chance you could call at 9:45 your time?

Ron Carleton
Counselor to the Administrator for Agricultural Policy

Sent from my iPhone

> On Mar 15, 2015, at 5:20 PM, DYKES, MICHAEL D [AG/1920] <michael.d.dykes@monsanto.com> wrote:
>
> Thank you Ron. I will give you a call tomorrow

>
> Michael
>
> Sent from my iPhone
>
>> On Mar 15, 2015, at 5:42 PM, Carleton, Ron <Carleton.Ron@epa.gov> wrote:
>>
>> Michael, you can call me at 10 your time. I'm in Wichita but can chat. **Ex. 6 - Personal Privacy**
>>
>> Ron Carleton
>> Counselor to the Administrator for Agricultural Policy
>>
>> Sent from my iPhone
>>
>>> On Mar 15, 2015, at 10:55 AM, DYKES, MICHAEL D [AG/1920] <michael.d.dykes@monsanto.com> wrote:
>>>
>>> Ron
>>> I want to thank you for the time you guy our 6 farmer guests in DC
>>> last week. The farm community has a lot of interest in the
>>> environmental policies that have the potential to impact their
>>> farming operations. They appreciated the discussion with you
>>>
>>>
>>> There is another matter that I would like to talk with you about. Would you be available for a brief conversation on Monday. I can call you if there is a time that is most convenient for you. Just let me know.
>>>
>>> Thank you
>>> Michael Dykes
>>>
>>> Sent from my iPhone
>>> This e-mail message may contain privileged and/or confidential
>>> information, and is intended to be received only by persons entitled
>>> to receive such information. If you have received this e-mail in error, please notify the sender immediately. Please delete it and all attachments from any servers, hard drives or any other media. Other use of this e-mail by you is strictly prohibited.
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To: Jones, Jim[Jones.Jim@epa.gov]
From: Sterling, Sherry
Sent: Wed 5/20/2015 10:35:32 AM
Subject: RE: HHS

Jim – he is Dr. Patrick Breysse. I have a general phone number, but it seems that everything there is closed until 8:00. I will keep trying….

From: Jones, Jim
Sent: Tuesday, May 19, 2015 5:50 PM
To: Sterling, Sherry
Subject: Fwd: HHS

Sherry. Can you get me the contact info for the head of NCEH at CDC. I believe that person is responsible for atsdr. Thx

Sent from my iPhone

Begin forwarded message:

From: "Housenger, Jack" <Housenger.Jack@epa.gov>
Date: May 19, 2015 at 4:50:11 PM EDT
To: "Jones, Jim" <Jones.Jim@epa.gov>
Subject: RE: HHS

Yes

Jess checked with them

They are

It is on the agenda for the general

It has been difficult to get information

From: Jones, Jim
Sent: Tuesday, May 19, 2015 4:33 PM
To: Housenger, Jack
Subject: Fwd: HHS

Monsanto thinks atsdr is doing a glyphosate
Assessment. Could you guys run that down?
Sent from my iPhone

Begin forwarded message:

From: "DYKES, MICHAEL D [AG/1920]" <michael.d.dykes@monsanto.com>
Date: May 19, 2015 at 3:28:05 PM EDT
To: Jim Jones <jones.jim@epa.gov>
Subject: HHS

Jim
We discussed briefly at the Ag Committee hearing the glyphosate review by the HHS Agency that was reviewing glyphosate and you were not aware of their review. Did you learn anything more about their efforts?

Thank you
Michael

Sent from my iPhone

To: Jones, Jim[Jones.Jim@epa.gov]; Wise, Louise[Wise.Louise@epa.gov]
Cc: Strauss, Linda[Strauss.Linda@epa.gov]
From: Mojica, Andrea
Sent: Tue 11/17/2015 2:18:04 PM
Subject: QFR follow up on glyphosate

....
;;;;
Jim,

It appears that our most recent statement on glyphosate was to BNA which was sent to OPA on October 8, 2015. The statement is as follows, "We are nearing completion of our cancer review which included consideration of the IARC review. We expect to release our draft risk assessment within the next few months."

However, before we were using the following statement which is what was referenced in the QFRs, "In 1991 EPA concluded that glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans) based on a lack of convincing carcinogenicity evidence and considering the criteria in EPA Guidelines for classifying a carcinogen. Since then, EPA has monitored emerging research on the carcinogenicity of glyphosate. In 2014, EPA reviewed over 55 epidemiological studies conducted on the possible cancer and non-cancer effects of glyphosate. Our review concluded that this body of research does not provide evidence to show that glyphosate causes cancer, and it does not warrant any change in EPA's cancer classification for glyphosate. This is the same conclusion reached in 2004 by the United Nations' Food and Agriculture Organization and affirmed this year by Germany's pesticide regulatory officials. In a few months, EPA will be releasing for public comment our preliminary human health risk assessment for glyphosate as part of our program to reevaluate all pesticides periodically. EPA is aware of the recent International Agency for Research on Cancer (IARC) report and will address it in detail in the preliminary risk assessment. Additional information regarding glyphosate and EPA's ongoing registration review can be found at:
http://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:31:0::NO:1,3,31,7,12,25:P3_XCHEMICAL_II
press responses contained the highlighted text.

Ex. 5 - Deliberative Process

Just as an FYI, below is the Washington Post article I was talking about. It uses the previous desk statement in the article.

Washington Post: October 4, 2015

∀ https://www.washingtonpost.com/lifestyle/food/its-the-chemical-monsanto-depends-on-how-dangerous-is-it/2015/10/04/2b8f58ee-67a0-11e5-9ef3-fde182507eac_story.html

∀ It's important to note that the IARC didn't do new research (that's not its job) but evaluated existing research. Other organizations, evaluating the same research, have reached different

conclusions. Although the Environmental Protection Agency's assessment of glyphosate, done in 1991, is woefully out of date (a new assessment is due this year), the agency last year took a fresh look specifically at cancer, in which it "reviewed over 55 epidemiological studies conducted on the possible cancer and non-cancer effects of glyphosate" and concluded that "this body of research does not provide evidence to show that glyphosate causes cancer. . . . This is the same conclusion reached in 2004 by the United Nations' Food and Agriculture Organization and affirmed this year by Germany's pesticide regulatory officials."

Andrea

To: Jones, Jim[Jones.Jim@epa.gov]
Cc: Wise, Louise[Wise.Louise@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]
From: Mojica, Andrea
Sent: Tue 11/17/2015 3:23:29 PM
Subject: RE: QFR follow up on glyphosate

;;;;;;
;;;;;;
Please see below for revised responses. Please let me know if you have any edits.

Thanks,

Andrea

∀ Question: Mr. Jordan - Recently, there has been some buzz about glyphosate's safety for use as a pesticide, due to the International Agency for Research on Cancer's classification, even though we have been using this product safely for decades, and there isn't a single regulatory agency worldwide that considers it to be a carcinogen. Does the EPA believe that glyphosate is safe to use within the prescribed label requirements?

Ex. 5 - Deliberative Process

∀ Mr. Jordan, opponents of biotechnology have been raising questions about the safety of glyphosate herbicide with certain GM crops, notwithstanding its **40-year history of safe use** and the fact that **no regulatory agency in the world considers glyphosate to be a carcinogen.** In April of this year, EPA issued a desk statement regarding glyphosate and the IARC conclusion. In this statement, EPA stated, in part: "In 2014, EPA reviewed over 55 epidemiological studies conducted on the possible cancer and non-cancer effects of glyphosate. Our review concluded that this body of research does not provide evidence to show that glyphosate causes cancer, and it does not warrant any change in EPA's cancer classification for glyphosate. This is the same conclusion reached in 2004 by the United Nations' Food and Agriculture Organization and affirmed this year by Germany's pesticide regulatory officials." *Can you confirm that this is the most recent public statement EPA has issued addressing the safety of glyphosate?*

Ex. 5 - Deliberative Process

From: Jones, Jim
Sent: Tuesday, November 17, 2015 10:16 AM
To: Mojica, Andrea
Cc: Wise, Louise ; Strauss, Linda
Subject: Re: QFR follow up on glyphosate

Ex. 5 - Deliberative Process

Sent from my iPhone

On Nov 17, 2015, at 9:18 AM, Mojica, Andrea <Mojica.andrea@epa.gov> wrote:

Jim,

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Ex. 5 - Deliberative Process

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? https://www.washingtonpost.com/lifestyle/food/its-the-chemical-monsanto-depends-on-how-dangerous-is-it/2015/10/04/2b8f58ee-67a0-11e5-9ef3-fde182507eac_story.html

? It's important to note that the IARC didn't do new research (that's not its job) but evaluated existing research. Other organizations, evaluating the same research, have reached different conclusions. Although the Environmental Protection Agency's assessment of glyphosate, done in 1991, is woefully out of date (a new assessment is due this year), the

agency last year took a fresh look specifically at cancer, in which it "reviewed over 55 epidemiological studies conducted on the possible cancer and non-cancer effects of glyphosate" and concluded that "this body of research does not provide evidence to show that glyphosate causes cancer. . . . This is the same conclusion reached in 2004 by the United Nations' Food and Agriculture Organization and affirmed this year by Germany's pesticide regulatory officials."

Andrea

To: Jones, Jim[Jones.Jim@epa.gov]
Cc: Wise, Louise[Wise.Louise@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]
From: Mojica, Andrea
Sent: Tue 11/17/2015 6:39:47 PM
Subject: RE: QFR follow up on glyphosate

.....
,,,,,,
Jim,

Ex. 5 - Deliberative Process

Andrea

From: Jones, Jim
Sent: Tuesday, November 17, 2015 10:26 AM
To: Mojica, Andrea
Cc: Wise, Louise ; Strauss, Linda
Subject: Re: QFR follow up on glyphosate

Ex. 5 - Deliberative Process

Sent from my iPhone

On Nov 17, 2015, at 10:23 AM, Mojica, Andrea <Mojica.andrea@epa.gov> wrote:

Ex. 5 - Deliberative Process

Andrea

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Ex. 5 - Deliberative Process

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Ex. 5 - Deliberative Process

From: Jones, Jim
Sent: Tuesday, November 17, 2015 10:16 AM
To: Mojica, Andrea <Mojica.andrea@epa.gov>
Cc: Wise, Louise <Wise.Louise@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Subject: Re: QFR follow up on glyphosate

Ex. 5 - Deliberative Process

Sent from my iPhone

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> Jim,
>
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the possible cancer and non-cancer effects of glyphosate. Our review concluded that this body of research does not provide evidence to show that glyphosate causes cancer, and it does not warrant any change in EPA's cancer classification for glyphosate. This is the same conclusion reached in 2004 by the United Nations' Food and Agriculture Organization and affirmed this year by Germany's pesticide regulatory officials. In a few months, EPA will be releasing for public comment our preliminary human health risk assessment for glyphosate as part of our program to reevaluate all pesticides periodically. EPA is aware of the recent International Agency for Research on Cancer (IARC) report and will address it in detail in the preliminary risk assessment. Additional information regarding glyphosate and EPA's ongoing registration review can be found at:
http://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:31:0::NO:1,3,31,7,12,25:P3_XCHEMICA
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Ex. 5 - Deliberative Process

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Andrea

To: Jones, Jim[Jones.Jim@epa.gov]
From: Dix, David
Sent: Fri 11/6/2015 2:46:54 PM
Subject: RE: materials for Tom B glyphosate meeting

;;;;
Thanks

Around all day, but am told you are booked!

We can catch up whenever you have a chance, today or next week.

David J. Dix, Ph.D.

Director, Office of Science Coordination and Policy

Office of Chemical Safety and Pollution Prevention

U.S. Environmental Protection Agency

1200 Pennsylvania Ave, NW (7201M)

Washington DC 20460

Email: dix.david@epa.gov

Office phone: 202-564-8429

Location: Room 4126A WJC East

From: Jones, Jim
Sent: Thursday, November 05, 2015 9:39 AM
To: Dix, David
Subject: FW: materials for Tom B glyphosate meeting

In case you haven't seen. Jim

From: Mojica, Andrea
Sent: Tuesday, November 03, 2015 12:19 PM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>
Subject: materials for Tom B glyphosate meeting

Jim,

Ex. 5 - Deliberative Process

Thanks,

Andrea

To: Jones, Jim[Jones.Jim@epa.gov]
From: Housenger, Jack
Sent: Tue 9/8/2015 11:25:41 AM
Subject: FW: GLY
Prof_Ivan Rusyn_EN .pdf
Catalogue of Questions - Fragenkatalog Öffentliche Anhörung_EN.pdf

....
,,,,
See the note from Ivan

Ex. 5 - Deliberative Process

From: Rusyn, Ivan [mailto:IRusyn@cvm.tamu.edu]
Sent: Monday, September 07, 2015 3:58 PM
To: Housenger, Jack
Cc: Dix, David
Subject: GLY

Dear Jack,

I hope you had a good summer and had a chance to look through the IARC monograph on glyphosate. Do let me know if there are any questions that you or your staff may have.

As you may know, there is quite a debate in Europe surrounding the BfR draft assessment report on glyphosate renewal. I was asked to appear at the hearings in Bundestag on September 28 (see attached invitation and a list of questions; I diid submit answers and they will be part of the public record after the hearing) and I am trying to catch up on where the government action is on this. I recall Jim Jones saying in an interview published by Reuters that EPA will release its re-assessment in July. Please let me know if that did in fact happen, or whether you have another date.

Also, you may be interested to know that a JMPR Expert Taskforce on Diazinon, Glyphosate and Malathion (http://www.who.int/entity/foodsafety/areas_work/chemical-risks/etc_final_new_1.pdf?ua=1) conclusions should be released very soon as the group finalized them last week.

Thank you and best regards,

Ivan

Ivan Rusyn, MD, PhD

Professor, Veterinary Integrative Biosciences
Texas A&M University

4458 TAMU

College Station, TX 77843-4458

Office: (979) 458-9866; Cell: (919) 624-2272

PubMed citations

Google Scholar page

http://rusynlab.org

http://comptox.us

List of questions for the hearing on 28 September 2015

1. What is the substantive basis for the different opinions which exist on the question of whether glyphosate is likely to be carcinogenic? How should these differences be viewed and what course of action will now be taken in this regard? What role does the fact that exposure varies depending on directions for use play in assessing the risks?
   What routes of exposure which could lead to an increased risk of cancer are relevant for Germany, with the directions for use currently in application?

2. How do you view the approval of active substances and plant protection products at European Union (EU) level and at national level? Should the existing legal requirement obliging companies applying for approval to make available and finance the necessary scientific studies be changed? And, if so, who should cover the costs? How many scientific studies on the possible carcinogenicity of glyphosate were assessed and did the studies apply to the active substance or to the plant protection product?

3. What alternative plant protection products are available to the agricultural sector to replace glyphosate and what environmental and health impacts would increased use of these products have? What would be the impacts on resistance management if glyphosate were no longer used? What would be the impacts on conservation tillage of replacing glyphosate?

4. What indications of other health hazards posed by glyphosate are you aware of, apart from the probable carcinogenic effects? Which institutions, particularly at international level, are investigating these indications of possible health hazards and what current international research projects assessing the possible health hazards posed by the active substance are you aware of?

5. A significant proportion of studies used by the Federal Institute for Risk Assessment (BfR) are financed or initiated by the chemical industry. What is your opinion of such studies and how do you view their findings?

6. To what extent should the monograph produced by the International Agency for Research on Cancer (IARC) influence the re-authorisation of glyphosate at EU level in your view and to what extent should the precautionary principle be applied regarding authorisation of glyphosate, against the background of studies concluding that glyphosate

is “probably carcinogenic”?

7. What impacts on the health of users, local residents and consumers in your opinion indicate that glyphosate ought not to be used in agriculture?

8. In your view, what impacts on the environment and on agriculture of the active substance glyphosate on the one hand and herbicide-resistant genetically modified plants on the other indicate that glyphosate ought not to be used as an active substance in agriculture?

9. What consequences would a ban on the use of glyphosate have on the agricultural sector in the EU and in countries which export agricultural commodities to the EU?

10. What differences are you aware of regarding the regulations, procedures and criteria applied in assessments by the IARC, Joint Meeting on Pesticide Residues (JMPR), Institute for Risk Assessment (BfR), European Food Safety Authority (EFSA) and, if applicable, the United States Environmental Protection Agency (EPA)? Which regulations may lead to scientific studies not being taken into account and how are the different conclusions reached by these institutions regarding the carcinogenicity of the active substance glyphosate to be viewed against this background?
(If you represent one of the institutions listed above, please indicate this to the *left* of the descriptions of the various regulations, procedures and criteria.)

11. How do you assess the current availability of data regarding the exposure of various groups in the population to glyphosate (with particular reference to professional and non-professional users, residents/bystanders/land users, consumers and children/infants)? In particular, how precisely can the level of (acute and background) exposure be assessed in your view and what (if any) recommendations do you have to improve the availability of data on glyphosate?

12. What consequences would adoption of the IARC classification as "probably carcinogenic to humans" have on the possible new authorisation of glyphosate as an active substance?
(c.f.:
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1272-20150601
p. 152 onwards, Annex 1, 3.6: Carcinogenicity)

Courtesy Translation

Professor Ivan Rusyn, MD
Texas A&M University
College of Veterinary Medicine and
Biomedical Sciences
College Station, Texas 77843
USA

By e-mail to:
IRusyn@cvm.tamu.edu

4 August 2015

Public hearing on Monday, 28 September 2015
List of questions

Dear Professor Rusyn,

Following your invitation from the Chairman of the Committee on Food and Agriculture, Mr Alois Gerig, to attend in an expert capacity the public hearing on the following topic

"Glyphosate: effects on the health of users and consumers, and potential consequences with regard to its approval as a pesticidal active substance"

please find attached the list of questions, as advised.

To allow the Committee members to prepare for the hearing, I would ask you to send your written statements on the twelve questions to the Committee Secretariat by **Wednesday, 9 September 2015,** if possible via e-mail to el-ausschuss@bundestag.de

Yours sincerely,

Margot Heimbach
Committee Secretariat

To: Jones, Jim[Jones.Jim@epa.gov]
Cc: Wise, Louise[Wise.Louise@epa.gov]
From: Mojica, Andrea
Sent: Fri 1/8/2016 8:40:00 PM
Subject: RE: glyphosate

It is unclear if the 1998 document was a full cancer review, but regardless the document still classifies glyphosate as Group E.

From: Mojica, Andrea
Sent: Friday, January 08, 2016 2:49 PM
To: Jones, Jim <Jones.Jim@epa.gov>
Cc: Wise, Louise <Wise.Louise@epa.gov>
Subject: glyphosate

Jim,

Attached is the glyphosate CARC document. Also, according to our October 30, 1991 *Second Peer Review of Glyphosate* we classified glyphosate as a Group E (evidence of non-carcinogenicity for humans). It appears that there was a review in 1998 as well. I am trying to locate this document to determine the classification.

Andrea

To: Jones, Jim[Jones.Jim@epa.gov]
Cc: Wise, Louise[Wise.Louise@epa.gov]
From: Mojica, Andrea
Sent: Fri 1/8/2016 7:49:28 PM
Subject: glyphosate
glyphosate CARC_1 Oct 2015.pdf

Jim,

Attached is the glyphosate CARC document. Also, according to our October 30, 1991 *Second Peer Review of Glyphosate* we classified glyphosate as a Group E (evidence of non-carcinogenicity for humans). It appears that there was a review in 1998 as well. I am trying to locate this document to determine the classification.

Andrea

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **October 1, 2015**

SUBJECT: **GLYPHOSATE:** Report of the Cancer Assessment Review Committee

PC Code: 417300	**DP Barcode:** N/A
Decision No.: N/A	**Registration No.:** N/A
Petition No.: N/A	**Regulatory Action:** N/A
Risk Assessment Type: NA	**Case No.:** N/A
TXR No.: 0057299	**CAS No.:** 1071-83-6
MRID No.: N/A	**40 CFR:** N/A

FROM: Jess Rowland,
Deputy Division Director
Chair, Cancer Assessment Review Committee
And
Karlyn Middleton, Co-Chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Charles Smith, Chief,
Risk Assessment Branch I
Health Effects Division (7509P)
And
Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division

On September 16, 2015, the Cancer Assessment Review Committee (CARC) of the Health Effects Division, of the Office of Pesticide Programs evaluated the carcinogenic potential of Glyphosate in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
Glyphosate

FINAL REPORT
October 1, 2015

CANCER **A**SSESSMENT **R**EVIEW **C**OMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S Environmental Protection Agency

Table of Contents

COMMITTEE MEMBERS IN ATTENDANCE:

Jess Rowland, M.S., Chair

Karlyn Middleton, M.S., Co-Chair

Gregory Akerman, Ph.D.

Lori Brunsman, B.S.

Jonathan Chen, Ph.D.

Anwar Dunbar, Ph.D.

Ray Kent, Ph.D.

Jessica Kidwell, M.S.

John Liccione, Ph.D.

Dannelle Lobdell, Ph.D., Epidemiologist, ORD

Nancy McCarroll, M.S.

Chris Schlosser, M.S.

Charles Wood D.V.M., Ph.D., Pathologist, ORD

EXECUTIVE SUMMARY

Glyphosate is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops.

In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division (HED), of the Office of Pesticide Programs (OPP), of the U.S. Environmental Protection Agency (USEPA) evaluated the carcinogenic potential of glyphosate. In accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* the CPRC classified glyphosate as a Group E Chemical: "Evidence of Non-Carcinogenicity for Humans" based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR# 0008897).

Earlier this year (March 2015), the International Agency for Research on Cancer (IARC), Lyon, France, assessed the carcinogenic potential of glyphosate. The IARC reviewed the available epidemiological studies and carcinogenicity studies for glyphosate in experimental animals. The IARC concluded that there is *limited evidence* in humans for the carcinogenicity of glyphosate based on a positive association for non-Hodgkin lymphoma (NHL). The IARC also concluded that there is *sufficient evidence* in experimental animals based on significant positive trends for kidney tumors in one study and for hemangiosarcomas in another study in male mice. IARC determined that there is strong evidence for genotoxicity. Overall, IARC classified glyphosate as "*probably carcinogenic to humans (Group 2A)* (IARC, 2015).

IARC's conclusion was based on epidemiologic studies available in the open literature and carcinogenicity studies in rats (4 studies) and mice (2 studies) by dietary administration. Of these six studies reviewed by IARC, two studies in rats and one study in mice were previously not available to OPP. The conclusion by IARC and the additional studies not available to OPP, prompted the agency to re-evaluate the carcinogenic potential of glyphosate.

On September 16, 2015, HED's Cancer Assessment Review Committee (CARC) evaluated all available epidemiological studies published in the open literature that examined the association between glyphosate exposure and one or more cancer outcomes. This included one cohort study, seven nested case-control studies based on the cohort study population, and 25 case- control studies. The CARC also evaluated 11 chronic toxicity/carcinogenicity studies in rats (7) and mice (4) following dietary administration for up to two years. Six of the studies (4 rat and 2 mouse) were submitted to OPP to support registration/re-registration requirements, including two studies in rats and one study in mice which were not previously available to OPP (but reviewed by IARC). Data for review of the other five studies (3 rat and 2 mouse) were obtained from a review article and its supplement published in the open literature (Greim *et al.,* 2015) that also had not been previously reviewed by the agency (IARC did not evaluate the five studies cited in the Greim *et al.* 2015 review article). The CARC also evaluated the mutagenicity/genotoxicity studies submitted to OPP as well as studies summarized in two review articles (Williams *et al*., 2000, and Kier and Kirkland, 2013) published in the open literature.

The CARC concluded that the epidemiological studies in humans showed no association between glyphosate exposure and cancer of the following: oral cavity, esophagus, stomach, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, brain (gliomas), soft-tissue sarcoma, leukemia, or multiple myelomas.

The CARC concluded that there is conflicting evidence for the association between glyphosate exposure and NHL. No association between glyphosate exposure and NHL was found in population-based case-control studies in the United States, Canada or France. Additionally, the large prospective Agricultural Health Study (AHS) with 54,315 licensed pesticide applicators in Iowa and North Carolina did not show a significantly increased risk of NHL. A population-based case-control study from Sweden suggested an association between glyphosate exposure and NHL; however, this finding was based on only 4 glyphosate-exposed cases and 3 controls.

When data from two case-control studies in Sweden (one on NHL and the other on hairy cell leukemia) were pooled, a univariate analysis showed an increased risk (odds ratio (OR) = 3.04; 95% confidence interval (CI) = 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, the risk was attenuated (OR=1.85; 95% CI=0.55–6.20). In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analysis showed an increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51). A meta-analysis of the six separate studies showed an association between glyphosate exposure and NHL with a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014). The CARC noted that most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and had risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data.

In an attempt to address the noted power/sample size issues across studies, IARC used adjusted weighting estimates of the two Swedish studies (Hardell *et al*. 2002 and Eriksson *et al*. 2008) and

reported an lower odds ratio in a second meta-analysis of the same data (OR=1.3; 95% CI=1.03–1.65). Given the limitations of the studies used and uncertainty in the analytical methods, the CARC concluded that a different weighting scheme could have resulted in a different meta risk ratio. Thus, while epidemiologic literature to date does not support a direct causal association, the CARC recommends that the literature should continue to be monitored for studies related to glyphosate and risk of NHL.

Overall, the CARC concluded that there was no evidence of carcinogenicity in the eleven carcinogenicity studies conducted in Sprague Dawley or Wistar rats and CD-1 mice. There were no treatment-related increases in the occurrence of any tumor type in either sex of either species.

By contrast, the IARC concluded that there is *sufficient evidence* in experimental animals based on a positive trend in the incidence of a relatively rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in CD-1 males in one feeding study. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. The CARC did not consider these tumors to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported non-neoplastic changes, were not statistically significant on pairwise analysis with concurrent control groups, and/or were within the range of the historical control data. If the kidney tumors and the hemangiosarcomas are really treatment-related, it is unlikely that the same tumors would not have been detected at higher incidences in the studies in the other studies of CD-1 mice when tested at similar or higher doses (1000–4000 mg/kg/day). Moreover, in 4 of the 11 studies (3 rat and 1 mouse) evaluated by CARC, there was no biologically or statistically significant increases in the occurrence of any tumor type in either species. The other observed differences in incidence did not show a dose response relationship, and were within the range of the background/historical control range. The four studies which were negative for carcinogenicity were reported in the review article by Greim *et al.* (2015) but were not included in the IARC evaluation. This omission of the negative findings from reliable studies may have had a significant bearing on the conclusion drawn for evidence of carcinogenicity in animals.

The CARC evaluated a total of 54 mutagenicity/genotoxicity studies which included studies submitted to the agency, as well as studies reported in the two review articles (Williams *et al.*, 2000, and Kier and Kirkland, 2013). A number of studies reported in the review article by Kier and Kirkland (2013) were not considered by IARC. The CARC, based on a weight-of-evidence of the *in vitro* and *in vivo* studies, concluded that there is no concern for genotoxicity or mutagenicity. Glyphosate was no mutagenic in bacterial reversion (Ames) assays or *in vitro* mammalian gene mutation assays. There is no convincing evidence that glyphosate induces micronuclei formation or chromosomal aberrations *in vitro* or *in vivo*.

By contrast, IARC's conclusion that glyphosate is genotoxic based on positive results that included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e.*, no purity information was provided). The IARC analysis also focused on DNA damage as an endpoint (*e.g.*, comet assay). DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA

changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited as positive findings for chromosomal damage had deficiencies in the design and/or conduct of the studies confounding the interpretation of the results. In addition these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. Furthermore, IARC's evaluation did not include a number of negative results from studies that were reported in the review article by Kier and Kirkland (2013). The inclusion of the positive findings from studies with known limitations, the lack of reproducible positive findings and the omission of the negative findings from reliable studies may have had a significant bearing on IARC's conclusion on the genotoxic potential of glyphosate.

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, based on the weight-of-evidence, glyphosate is classified as "Not Likely to be Carcinogenic to Humans". This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk/odd ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis with concurrent control groups, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

I. INTRODUCTION

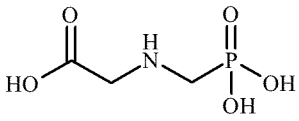
On September 16, 2015 the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of glyphosate.

II. BACKGROUND INFORMATION

Glyphosate (*N*-(phosphonomethyl) glycine) is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops. Tolerances are currently established for residues of glyphosate in/on various plant commodities at 0.2–400 ppm (40 CFR §180.364 (a)) (1). Registered uses range from tree nuts, citrus, and grapes to corn, soybeans, cotton, and rice. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Aquatic and terrestrial registered uses of glyphosate include non-selective control of nuisance aquatic weeds, ornamentals, greenhouses, residential areas, ornamental lawns and turf, fallow land, pastures, and nonagricultural rights-of-way.

The chemical structure and nomenclature for glyphosate is presented in Table 1.

Table 1. Chemical Nomenclature of Glyphosate

Compound	
Common name	Glyphosate
Company experimental name	DPX-B2856
IUPAC/CAS name	*N*-(phosphonomethyl)glycine
CAS registry number	1071-83-6

Glyphosate is formulated in liquid and solid forms, and it is applied using ground and aerial equipment. Application rates of glyphosate to food crops range from <1 pound (lb) of acid equivalent (ae) per acre (A) for a variety of crops to approximately 15 lb ae/A for spray and spot treatments of crops including tree nuts, apples, citrus, and peaches. Residential lawn and turf application rates range from <1 lb ae/A to approximately 10.5 lb ae/A. The application timing of glyphosate is varied. Glyphosate can be applied early and late in the season, at pre-plant, planting, pre-emergence, pre-bloom, bud stage, pre-transplant, pre-harvest, post-plant, post-transplant, post-bloom, and post-harvest. It can also be applied during dormant stages and to fallow land, established plantings, stubble, and when needed. In September 1993, the agency issued the glyphosate Reregistration Eligibility Decision (RED) document (D362745), available from http://www.epa.gov/pesticides/reregistration/REDs/old_reds/glyphosate.pdf.

In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division, Office of Pesticide Programs, in accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* classified glyphosate as a Group E Chemical: Evidence of Non-Carcinogenicity for Humans. This classification was based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR No. 0008897).

In 2002, the European Union (EU) concluded that there was no evidence of carcinogenicity for glyphosate in long-term studies with mice and rats (EU, 2002).

In 2004, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that there was no evidence of carcinogenicity for glyphosate in long term studies in mice and rats and there was no evidence for genotoxic potential (JMPR, 2004).

In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as a Group 2A chemical (Probable Human Carcinogen) based on *limited evidence* of carcinogenicity in humans and sufficient evidence in experimental animals. The limited evidence in humans was based on a positive association between non-Hodgkin lymphoma (NHL) and glyphosate exposure from published epidemiology studies. The *sufficient evidence* in experimental animals was based on a positive trend in the incidence of renal tubular carcinoma and renal tubule adenoma/ carcinoma combined in male CD-1 mice in one study and on a positive trend in the incidence of hemangiosarcomas in male CD-1 mice in another study. There is strong evidence that glyphosate causes genotoxicity (IARC, 2015).

In 2015, two chronic toxicity/carcinogenicity studies in rats (MRID Nos. 49631701; 4970460) and one carcinogenicity study in mice (MRID No. 49631702) that were reviewed by IARC, but not previously available to OPP, were submitted and reviewed. This assessment by the CARC includes all of the studies (epidemiology and animals) reviewed by IARC as well as a subset of animal studies reported in a review article by Greim *et al.* (2015) but not reviewed by IARC.

III. EPIDEMIOLOGY

This section includes a review of epidemiologic cohort and case-control studies of glyphosate to evaluate whether exposure to glyphosate is associated causally with the risk of developing cancer in humans.

The Agricultural Health Study (AHS) is a large prospective study conducted in Iowa and North Carolina. Participants (private and commercial applicators) were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying pesticides (including glyphosate), and frequency (days of use per year) and duration (years of use) of pesticide use. Data on the use of personal protective equipment, other farming practices, dietary and lifestyle information, demographic data, and medical information were also collected via the questionnaire (Alavanja *et al.,* 1996). The role of pesticide use and lymph hematopoietic cancers, and in particular NHL, has been studied in several investigations. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available (De Roos *et al.*, 2005); however, for NHL and other non-solid tumors, several investigations are published.

A. Cohort Study

There are multiple published studies which use data from the same cohort, the AHS (Alavanja *et al.,* 2003; Flower *et al.*, 2004; De Roos *et al.*, 2005; Engel *et al.*, 2005; Lee *et al.*, 2007; Landgren *et al.*, 2009; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010). It should be noted that there is some overlap between the cases and person-time reported findings in the AHS.

B. Case-Control Studies

Three case-control studies conducted by the National Cancer Institute in Iowa and Minnesota during the 1980s were reported by Brown *et al.* (1990), Cantor *et al.* (1992) and Brown *et al.* (1993).

De Roos *et al.* (2003) and Lee *et al.* (2004a) reported the results of case-control studies conducted in Iowa, Minnesota, Nebraska and/or Kansas in the U.S.A.

The Canadian population based case-control studies were reported by McDuffie *et al.*, 2001; Hohenadel *et al.*, 2011; Karunanayke *et al.*, 2012; and Kachuri *et al.*, 2013.

Results of the Swedish case-control studies were reported by Nordstrom *et al.*, 1998; Hardell and Erikson, 1999 and Hardell *et al.*, 2002; and Eriksson *et al.*, 2008.

A single case-control study conducted in France was reported by Orsi *et al.* (2009).

Coco *et al.*, (2013) reported the results of a pooled analyses of case-control studies conducted in six European countries between 1998 and 2004.

Case-control studies on the cancer of the brain (mainly gliomas) were reported by Ruder *et al.* 2004; Carreon *et al.*, 2005; Lee *et al.*, 2005; and Yiin *et al.*, 2012.

Case-control studies on other cancer sites were reported by Alavanja *et al.*, 2004 (lung); Bank *et al.*, 2011 and Koutros *et al.*, 2013 (prostate); Pahwa *et al.*, 2012 (soft tissue sarcoma) and Lee *et al.,* 2004b (stomach and esophagus).

Schinasi and Leon (2014) conducted a meta-analysis of the six studies that evaluated NHL and glyphosate exposure (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; DeRoos *et al.*, 2003; 2005; Eriksson *et al.*, 2008; and Orsi *et al.*, 2009). Sorahan (2015) conducted a re-analysis of the multiple myeloma in the U.S. AHS.

C. Results

A summary of the studies evaluating the association between glyphosate exposure and cancer are discussed below.

- Results of the studies reporting data on solid tumors (non-lymphohematopoietic) at various anatomical sites are presented in Table 2.

- Results of the studies reporting data on glyphosate exposure and non-solid tumors (lymphohematopoietic) are presented in Table 3.

1. Solid Tumor Cancer Studies

Within the AHS study cohort, a number of authors evaluated several anatomical cancer sites in relation to pesticide use. A discussion of studies outside of the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in Section C.2. (Non-Solid Tumor Sites).

(i) Cancer at Multiple Sites

De Roos *et al.*, (2005) evaluated associations between glyphosate exposure and cancer incidence in the AHS cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. The authors used Poisson regression to estimate exposure-response relationships between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Exposure to glyphosate was not associated with all cancers combined [Rate Ratio (RR) =1.0 with 95% Confidence Interval (CI) of 0.90–1.2)] or any cancer at a specific anatomical site.

Several AHS nested case-control analyses as well as the cohort analysis from De Roos *et al.*, 2005, also provide information concerning the carcinogenic potential of glyphosate. As presented in Table 2, there is no statistical evidence of an association with glyphosate presented across these studies. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and cancers of the oral cavity (De Roos *et al.*, 2005), colon (De Roos *et al.*, 2005; Lee *et al.*, 2007), rectum (De Roos *et al.*, 2005; Lee *et al.*, 2007), lung (De Roos *et al.*, 2005), kidney (De Roos *et al.*, 2005), bladder (De Roos *et al.*, 2005), pancreas (De Roos *et al.*, 2005; Andreotti *et al.*, 2009), breast (Engel *et al.*, 2005), prostate (Alavanja *et al.*, 2003; Koutros *et al.*, 2013) or melanoma (De Roos *et al.*, 2005; Dennis *et al.*, 2010). The risk ratios (OR) or rate ratios (RR) and 95% confidence interval (CI) for these studies are provided in Table 2.

In a population-based study (Band *et al.*, 2011) outside of the AHS, Canadian researchers reported non-significantly elevated odds of prostate cancer in relation to glyphosate use (OR=1.36; 95% CI=0.83–2.25). This study included prostate cancer cases from 1983-1990, prior to the prostate-specific antigen (PSA) era. Consequently, the study included more advanced tumors before diagnosis. Additionally, these data are in conflict with the results of Alavanja *et al.* (2003), which reflects the PSA-era cases (*i.e.*, cases which are typically identified at an earlier stage in the progression of the disease). Koutros *et al.* (2013) did not identify an association with advanced prostate cancer (OR=0.93; 95% CI=0.73–1.18) in a prostate cancer follow-up study within the AHS.

A Canadian case-control study (Pahwa *et al.*, 2011) examined exposure to pesticides and soft tissue sarcoma and found no relation with the use of glyphosate (OR=0.90; 95% CI= 0.58–1.40).

Flower *et al.* (2004) examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with maternal use exposure to glyphosate (OR=0.61; 95% CI= 0.32–1.16) or paternal (prenatal) exposure to glyphosate: (OR=0.84; 95% CI= 0.35– 2.54).

(ii) Brain (Glioma) Cancer

Lee *et al.* (2005) investigated the association between brain cancer with farming and agricultural pesticide use. The authors conducted telephone interviews of men and women diagnosed with gliomas (n=251) between 1988 and 1993 in Nebraska and in controls (n=498) identified from the same regions. Matching for age and vital status, study authors reported a non-significant elevated odds of glioma (OR=1.5; 95% CI=0.7–3.1) in relation to glyphosate use; however, the results were significantly different between those who self-reported pesticide use (OR=0.4; 95% CI=0.1–1.6), and for those for whom a proxy respondent was used (OR=3.1; 95% CI=1.2–8.2), indicating recall bias was likely a characteristic of this study.

Three population-based case-control studies evaluated the risk of brain cancer, specifically, glioma risk, among men and women participating in the Upper Midwest Health Study (Carreon *et al.*, 2005; Ruder *et al.*, 2004; Yiin *et al.*, 2012). Ruder *et al.* (2004) reported no association between brain cancer and glyphosate use, but did not present any specific results (*i.e.* quantitative data). Among glioma cases identified 1995–1997 by Carreon *et al.* (2005), the authors found little evidence of a role for glyphosate in the etiology of this tumor. Herbicide use, including glyphosate was not associated with glioma in women by proxy respondents (OR=0.75; 95% CI=0.4–1.3) or excluding proxy respondents (OR=0.6; 95% CI=0.3–1.2). In the study by Carreon *et al.* (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to Lee *et al.* (2005). Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), the authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (home and garden use: OR=0.98; 95% CI=0.67–1.43; non-farm jobs: OR=0.83; 95% CI=0.39–1.73) (Yiin *et al.*, 2012).

(iii) Stomach and Esophageal Cancers

In a population-based case control study in eastern Nebraska, Lee *et al.* (2004) investigated pesticide use and stomach and esophageal adenocarcinomas. Cancer cases (stomach=170 and esophagus=137) were identified through the state cancer registry, and confirmed by a pathologist. The exposure assessment was based on self-reported pesticide use, with follow-up telephone interview to verify the reported information. There was no association between glyphosate exposure and either stomach cancer (OR=0.8; 95% CI=0.4–1.5) or esophageal cancer (OR=0.7; 95% CI=0.3–1.4).

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Cancer at Multiple Sites					
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	All cancers RR =1.0 (0.9-1.2)	No association between glyphosate exposure and all cancer including NHL	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)
Site-Specific Cancers: Lung; Oral cavity; Colon; Rectum; Kidney; Bladder; Prostate and Melanoma					
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	Lung RR= 0.9 (0.6-1.3) Oral Cavity RR=1.0 (0.5-1.8) Colon RR=1.4 (0.8-2.2) Rectum RR=1.3 (0.7-2.3) Pancreas RR=0.7 (0.3-2.0) Kidney RR=1.6 (0.7-3.8) Bladder RR=1.5 (0.7-3.2) Prostate RR=1.1 (0.9-1.3) Melanoma RR=1.6 (0.8-3.0)	No significant association between glyphosate exposure and cancer of the lung, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate or melanomas	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Breast Cancer					
Engel *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 30,454 wives of licensed pesticide applicators with no history of breast cancer at enrollment	Self-report questionnaire	Direct exposure (wives who applied) OR=0.9 (0.7-1.1) (Exposed: 82 cases, 10,016 controls) Indirect exposure (wives whose husbands applied) OR=1.3 (0.8-1.9) (Exposed: 109 cases, 9,304 controls)	No association between glyphosate exposure and breast cancer	Age, race and state of residence (Iowa and North Carolina). Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Pancreatic Cancer					
Andreotti *et al.* (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; follow-up to 2004 93 cases 82,503 controls	Self-report questionnaire; validated, reliability tested	Ever-use OR=1.1 (0.6, 1.7) (Exposed: 55 cases)	No association between glyphosate exposure and pancreatic cancer	Age, smoke, diabetes, applicator type. Limited to licensed applicators. Potential exposure to multiple pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Prostate Cancer					
Alavanja *et al.* (2003) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; cancer thru 1999 55,332 male applicators	Self-report questionnaire; validated, reliability tested	No quantitative risk estimate reported	No quantitative estimate due to lack of significant exposure-response association with prostate cancer.	Age, family history. Limited to licensed applicators. Potential exposure to multiple pesticides
Band *et al.* (2011) British Columbia, Canada	Case-Control 1983- 1990 1,516 prostate cancer patients 4,994 age-matched controls	Job exposure matrix for agriculture; detailed occupational history; exposure aggregated over all jobs reported. 60 exposed cases	OR=1.36 (0.83-2.25) (Exposed: 25 cases 60 controls)	No association between glyphosate exposure and prostate cancer	Alcohol consumption, cigarette years, education level, pipe smoking years and respondent
Koutros *et al.* (2013) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2003 1,962 incident cases, including 919 aggressive prostate cancers among 54,412 applicators	Self-report questionnaire, validated	OR=0.93 (0.73-1.18)	No association between glyphosate exposure and prostate cancer	Age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Colorectal Cancer					
Lee *et al*. (2007) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-97; follow-up to 2002 56,813 licensed pesticide applicators	Self-report questionnaire	Colon OR=1.0 (0.7-1.5) (Exposed: 151 cases 49 controls) Rectum OR=1.6 (0.9-2.9) (Exposed: 74 cases 18, controls) Colorectal OR=1.2 (0.9-1.6) (Exposed: 225 cases 67 controls)	No significant association between glyphosate exposure and colon, rectum or colorectal cancer	Age, smoking, state, total days use pesticides. Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Cutaneous Melanoma					
Dennis *et al.* (2010) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 150 cases, 24,554 non-cases	AHS self-report questionnaire	No quantitative risk estimate reported	No quantitative estimate due to lack of an association with cutaneous melanoma	Age, sex, tendency to burn, red hair, sun exposure time, BMI at 20 years

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Soft Tissue Sarcoma					
Pahwa *et al.* (2011) Canada	Case-Control 1991-1994 342 cases, 1506 age/resident matched controls	Self-reported use, structured interview/ questionnaire; cumulative exposure (+/-10 days/yr)	OR=0.90 (0.58-1.40)	No association between glyphosate exposure and soft tissue sarcoma	Significant medical history variables and with strata for the variables of age group and province of residence
Total Childhood Cancer					
Flower *et al.* (2004) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control; hybrid prospective/ retrospective 1993-1998 21, 375 children of licensed pesticide applicators In Iowa (n=17,357) North Carolina (n=4018)	Self-report questionnaire; duration and frequency of pesticide use; Female Family questionnaire (child name)	<u>Maternal use</u> OR=0.61 (0.32-1.16) 32 cases <u>Paternal use (prenatal)</u> OR=0.84 (0.35-2.34);	No association was detected between frequency of parental pesticide application of glyphosate and childhood cancer risk.	Potential exposure to other pesticides. Child age in multiple logistic [standardized incidence ratio (SIR)] was unadjusted

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Brain Cancer (Glioma)					
Lee *et al.* (2005a) Nebraska	Population based Case-Control study 1988-1993; 251 glioma cases 498 controls	Self-reported questionnaire information, telephone follow-up for unclear responses; men and women assessed separately	Self-Report OR=0.4 (0.1- 1.6) (Exposed: 4 cases 17 controls) Overall OR=1.5 (0.7-3.1) (Exposed: 17 cases 32 controls) Proxy report OR=3.1 (1.2- 8.2) (Exposed:13 cases 15 controls)	Non-significant excess risk for the overall group, but inconsistent for self-report and proxy indicating recall bias	Age, proxy, respond type
Ruder *et al.* (2004) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin, U.S.A.)	Population-based Case-Control 1995-1997 457 glioma cases 648 population controls	Self-report questionnaire, with telephone based follow-up	No quantitative risk estimate reported for glyphosate.	No association with glyphosate exposure and brain cancer	Farm residence, age, use of other pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Carreon *et al.* (2005) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 341 glioma cases, 528 controls	Self-report questionnaire	Proxy respondents OR=0.75 (0.4-1.3) (Exposed: 18 cases 41 Controls) Excluding proxy OR=0.6 (0.3-1.2) (Exposed:10 cases)	No association with glyphosate exposure and brain cancer	Age, education and use of other pesticide
Yin et al. (2012) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 798 glioma cases 1,175 controls	Self-report questionnaire	Home/garden use OR=0.98; 95% CI=0.67 - 1.43; Non-farm jobs: OR=0.83; 95% CI=0.39-1.73)	No significant positive association with glyphosate exposure and brain cancer	Age, sex, education and use of other pesticide

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Esophagus and Stomach Cancer					
Lee *et al*. (2004b) Nebraska, U.S.A.	Population based Case-Control 1988-1993 137 esophageal cases; 170 stomach cases; 502 controls	Self-report pesticide use, telephone structured interview	Esophagus OR=0.7 (0.3-1.4) (Exposed:12 cases 46 controls) Stomach OR=0.8 (0.4-1.5) (Exposed: 12 cases 46 controls)	No association with glyphosate exposure and esophagus or stomach cancer	Age, sex

2. Non-Solid Tumor Cancer Sites

A number of studies evaluating the possible link between pesticide use and lymphohematopoietic cancers such as leukemia, multiple myeloma and NHL are presented in Table 3.

(i) Leukemia

In a population-based case-control study in Iowa and Minnesota, Brown *et al.* (1990) investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR=0.9; 95% CI=0.5–1.6). The study population (578 cases; 340 living and 238 deceased and 1245 controls) was identified from cancers reported to state registry or authorities in 1981–1984, and the pesticide exposure assessment was performed through in-person interviews which the authors state likely reduced the exposure misclassification (*i.e.* incorrect exposure information). Although the large sample size is a strength of this study, the limitations include not controlling for exposure to other pesticides, limited power for studying the effects of glyphosate use, and the potential for recall bias.

In a Swedish population-based case-control study, 121 cases in men and 484 controls matched for age and sex were identified in 1987–1992 through the Swedish cancer registry. The authors reported a non-statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR=3.1; 95% CI=0.8–12.0), controlling for age, sex, and residential location. However, because these results are based on only 4 glyphosate-exposed cases and 5 exposed controls as noted by the authors, this risk should be interpreted with caution. Also, there was limited power to detect an effect and there was no adjustment for other exposures. At this time, there is limited available literature concerning glyphosate use and leukemia (Nordstrom *et al.*, 1998).

(ii) Multiple Myeloma

In a follow-up analyses using the same study population from Iowa and Minnesota Brown *et al.* (1993) investigated whether pesticide use is also related to multiple myeloma. Among men in Iowa (173 cases, 605 controls), the authors observed a statistically non-significant elevated association with glyphosate use (OR=1.7; 95% CI=0.8–3.6). However, the authors caution that while the study may lend support to the role of pesticides in general, the study limitations preclude use of the evidence as a definitive finding for any one compound.

De Roos *et al.* (2005) reported a suggestive association between multiple myeloma and glyphosate-exposed pesticide applicators based on a small number (32) of cases. For applicators with the full data set (54,315) and without adjustment for other variables the OR was 1.1; 95% CI=0.5–2.4. In the fully adjusted model, there was a non-statistically significantly elevated risk (OR=2.6; 95% CI=0.7–9.4), however, the number of participants included in this analysis was lower (n=40,716) due to missing data for the covariates. The authors postulated that the increased myeloma risk could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses.

Sorahan (2015), using Poisson regression, re-analyzed the AHS data reported by De Roos *et al.* (2005) to examine the reason for the disparate findings in relation to the use of a full data set versus the restricted data set. Risk ratios were calculated for exposed and non-exposed subjects. When adjusted for age and sex, the OR was 1.12 with the 95% CI of 0.5–2.49 for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of other pesticides did not have any effect (OR=1.24; 95% CI=0.52–2.94).

In a population-based case-control study among men in six Canadian provinces between 1991 and 1994, researchers reported non-statistically significantly elevated odds of multiple myeloma in relation to glyphosate use (OR=1.22; 95% CI=0.77–1.93), based upon 32 glyphosate exposed multiple myeloma case and 133 controls (Pahwa *et al.*, 2012).

Kachuri *et al.* (2013), using the same Canadian study population as above, further explored multiple myeloma in relation to days per year glyphosate used in 342 cases of multiple myeloma and 1357 controls. For ever use, the OR=1.19 and 95% CI=0.76–1.87. For light users (≤2 days/year) there was no association (OR=0.72; 95% CI=0.39–1.32; 15 exposed cases); whereas, for heavy users (>2 days/ year), there was a non-significant increased odds ratio (OR=2.04; 95% CI=0.98–4.23; 12 exposed cases). The limitation in this study was the same as the previous study (*i.e.*, the number of cases and controls exposed to glyphosate were very low).

Landgren *et al.* (2009), within the AHS study population, investigated the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS). The MGUS is considered a pre-clinical marker of multiple myeloma progression. The authors did not observe a link with glyphosate use in the AHS cohort (OR=0.50; 95% CI=0.20–1.0).

(iii) Lymphoma

The National Cancer Institute (NCI) performed a series of population-based case-control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred non-Hodgkin lymphoma (NHL) cases and controls, the identified cases were through disease registries which in many cases, were histopathologically confirmed. The investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time.

Cantor *et al.* (1992), in a case-control study of NHL interviewed a total of 622 white men and 1245 population based-controls in Iowa and Minnesota. Only 26 cases and 49 controls ever handled glyphosate yielding an OR of 1.1 with the 95% CI of 0.7–1.9. The study, however, did not adjust for exposure to other pesticides.

De Roos *et al.* (2003) used pooled analysis (n=3,417) of three case-control studies of NHL conducted in white men in Nebraska, Kansas and in Iowa and Minnesota. Based on 36 exposed cases and 61 exposed controls, the risk estimates for the association between glyphosate exposure and NHL was significant (OR=2.1; 95% CI=1.1–4.0) in the logistic regression analyses. However,

utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, there was an increase risk, but the increase was not statistically significant (OR=1.6; 95% CI=0.90–2.8). Overall, the data showed a suggestive association.

Based on the above findings, Lee *et al*., (2004) examined the relationship between asthma and pesticide exposure, and NHL. Pooling data from several midwestern states (IA, MN, and NE) increased the study sample size, and additional pesticide use information was incorporated to adjust the risk estimate (duration and frequency of use, telephone follow-up interview). The study included 872 men with NHL and 2381 frequency-matched controls. The authors reported that the OR associated with glyphosate was not statistically significantly different among those with asthma (OR=1.2; 95% CI=0.4–3.3; 6 exposed cases) and among those without asthma (OR=1.4; 95% CI=0.98–2.1; 53 exposed cases), adjusting for age, state and vital status.

The three studies discussed above (Cantor *et al*., 1992; De Roos *et al*., 2003 and Lee *et al*., 2004) reflect the same population in the AHS and used different levels of information (duration and frequency of exposure) and different analytic techniques [hierarchical regression and stratified analysis (by atopy)]. While studies with increasing levels of refinement to methodology report a stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

A population-based case–control study (Hardell and Erickson, 1999) investigated the exposure to pesticides as a risk factor for NHL in Sweden during 1987–1990. Exposure data were ascertained by comprehensive questionnaires and supplemented by telephone interviews. Of the 404 cases and 741 controls, only 4 glyphosate-exposed cases and 3 controls were included in the study. In a univariate analysis, the risk estimate was elevated, but precision was low (OR=2.3; 95% CI=0.40–13.0).

Hardell *et al*. (2002) analyzed pooled data from two case-control studies from Sweden that examined NHL (Hardell and Erickson, 1999) and another on hairy cell leukemia, a subtype of NHL (Nordstrom *et al*., 1998). In the univariate analysis glyphosate exposure was found to be significantly increased (OR=3.04; 95% CI=1.08–8.52) but, when study site, and vital status were considered in a multivariate analyses, there was a non-statistically elevated risk among glyphosate users (OR=1.85; 95% CI=0.55–6.20). However, the wide range of the CI suggest that the study is under powered and, therefore the findings do not allow definitive conclusion on the association of NHL and glyphosate exposure.

In another case-control study in Sweden (1999–2003), Eriksson *et al*. (2008) examined the effects of exposure to different agents and NHL among 910 NHL cases and 1016 non-NHL controls. Glyphosate exposure which was reported in 29 cases and 18 controls produced an OR of 2.02 (95% CI=1.10–3.71) in a univariate analysis and an OR of 1.51 (95% CI=0.77–2.94) in a multivariate analysis conducted to clarify the relative importance of exposure to different pesticides. When exposure was for more than 10 days/year, the OR was 2.36 (95% CI=1.16–4.40)

and for exposure less than 10 days/year, the OR was 1.69 (95% CI=0.7–4.07). The risk estimate was elevated also for B-cell lymphoma and glyphosate exposure (OR=1.87; 95% CI=0.998–3.51).

McDuffie *et al.* (2001) in a multicenter-population based study among men of six Canadian provinces estimated the association between glyphosate and NHL. The study included 517 cases and 1506 controls identified betwen1991and 1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of cases, implemented a two-tiered exposure questionnaire; and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the test results. There was a non-statistically significant increased risk of NHL from glyphosate exposure. The OR was 1.26 and the 95% CI was 0.87–1.80 for 51 exposed cases, adjusted for age and province and the OR was 1.20 with a 95% CI of 0.83–1.74 when adjusted for age, province and high-risk exposure (adjusted for statistically significant medical variables such as history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative).

In a follow-up study which controlled for exposure to other pesticides, the risk to NHL from glyphosate exposure was attenuated. Glyphosate exposure which was reported in 19 cases and 78 controls produced an OR of 0.92 with 95% CI of 0.54–1.55 (Hohenadel *et al.*, 2011). Within this series of studies, the authors also evaluated Hodgkin lymphoma (HL), and observed little statistical evidence of an association, using similar study design and methods. Among the 38 cases exposed to glyphosate the OR was 0.99 with a 95% CI of 0.62–1.56 (Karunanayake *et al.,* 2012).

In a hospital-based case control study conducted between 2000 and 2004 in France, authors identified 491 NHL cases and 456 age-and sex-matched controls, and performed telephone-based questionnaire to assess pesticide and other confounding variables. There was no association between NHL and glyphosate use; for the 12 exposed cases, the OR was 1.0 and the 95% CI was 0.5–2.2). For Hodgkin lymphoma, for the 6 exposed cases, the OR was 1.7 and the 95% CI was 0.6–5.0 (Orsi *et al*., 2009).

The EPILYMPH case-control study was conducted across six countries in Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain) to explore the role of occupational exposure to specific chemicals and risk of lymphoma overall, B-cell lymphoma and other subtypes. Although the study recruited 2348 cases and 2462 controls, only a very small number of cases were exposed to glyphosate (n=4) and controls (n=2). A non-significant increase in OR was observed for B-cell lymphoma (OR=3.1; 95% CI=0.6–17.1), but the estimate is unstable due to the small number of exposed cases and controls (Cocco *et al.,* 2013)

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL using data from six of the above mentioned studies (McDuffie *et al*., 2001; Hardell *et al*., 2002; DeRoos *et al*., 2003 and 2005; Eriksson *et al*., 2008; and Orsi *et al*., 2009). Since the authors identified a variety of sources of heterogeneity between publications, they calculated meta-risk ratio (RR) estimates and 95% CIs using random effect models, allowing between study heterogeneity to contribute to the variance. They reported I^2 values, which represented the

percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency. For glyphosate, the meta-risk ratio was 1.5 with a 95% CI of 1.0–2.0 and the I^2 value was 32.7% indicating greater inconsistency in these data sets. This study combined multiple smaller studies that on their own were very limited in statistical power to detect differences.

The 2015 IARC evaluation noted that fully adjusted risk estimates in two of the Swedish studies (Hardell *et al.*, 2002 and Eriksson *et al.*, 2008) were not used in the analysis conducted by Schinasi and Leon (2014). Consequently, IARC conducted a reexamination of the results of these studies. For an association between glyphosate exposure and NHL, the IARC estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65), I^2=0%; p=0.589 for heterogeneity) (IARC 2015).

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Leukemia					
Brown *et al.* (1990) Iowa and Minnesota, U.S.A.	Population-based Case-Control 1981-1984 578 cases 1245 controls	In person interview; surrogates used.	OR=0.9 (0.5-1.6) (Exposed:15 cases 49 controls)	No association between glyphosate exposure and leukemia	Vital status (alive, dead), residency (IA or MN), tobacco use, parent, sibling, or child with a lymphopoietic cancer, high risk occupation and exposure to substances (benzene, hair dyes etc) related to risk of leukemia
Nordstrom *et al.* (1998) Sweden	Population-based Case-Control 1987-1992 121 cases 484 controls	Self-reported pesticide questionnaire and follow-up telephone interview	OR=3.1 (0.8-12) (Exposed: 4 cases 5 controls)	A non-statistically significant elevated risk of hairy cell leukemia	Age, sex, country of residence (selected using matching, dissolved matching analyses) No adjustment for exposure from other pesticides
Multiple Myeloma					
Brown *et al.* (1993) Iowa, U.S.A.	Population based Case-Control 1981-1984 173cases 650 controls	Interview based questionnaire with follow-up	OR=1.7 (0.8-3.6) (Exposed: 11 cases 40 controls)	Limited power to assess association of glyphosate exposure and multiple myeloma	Age and vital status

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
De Roos *et al*. (2005) Iowa and North Carolina, U.S.A.	Prospective Cohort 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	Full data set RR =1.1 (0.5-2.4) (Exposed: 32 cases) Adjusted for age etc RR=2.6 (0.7-9.4)	No risk for full data set. Excess risk only with no missing information of 22 cases in the restricted data set (Sorahan, 2015)	Missing data on covariates when multiple adjustments were made, limiting interpretation
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=2.4 (0.8-7.3) (Exposed: 5 cases 18 controls)	No significant association with glyphosate exposure and multiple myeloma	Age, center, socioeconomic category
Pahwa *et al*. (2012) Canada	Population based Case-Control 1991-1994 342 cases 1506 controls	Self-reported pesticide use, structured interview with questionnaire; cumulative exposure (+/-10 days/yr)	OR=1.22 (0.77-1.93) (Exposed: 32 cases 133 controls)	No significant association with glyphosate exposure and multiple myeloma	Significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age group and province of residence

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Kachuri *et al.* (2013) Canadian Provinces	Population based Case-Control 1991-1994 342 cases 1357 controls	Self-administered questionnaire	For ever use OR=1.19 (0.76-1.87) Exposed: 32 cases 121controls Light (<2 d/yr) use OR=0.72 (0.39 -1.32) Exposed: 15 cases 88 controls Heavy (>2 d/yr) use OR=2.04 (0.98-4.23) Exposed: 12 cases 29 controls	No association with glyphosate exposure and multiple myeloma for ever or light users Increase for heavy users is non-significant	Relatively low response rate
Monoclonal Gammopathy of Undetermined Significance (MGUS)					
Landgren *et al.* (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 678 participants	Self-administered questionnaire	OR=0.5 (0.2-1.0)	No association with glyphosate exposure and MGUS, a premalignant disorder that often precedes multiple myeloma	Age and education

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Non-Hodgkin Lymphoma (NHL)					
Cantor *et al.* (1992) Iowa and Minnesota, U.S.A.	Population based Case-Control 1980-1983 622 cases 1245 controls	Structured interview, questionnaire response; farm activities and specific pesticide use	OR=1.1 (0.7-1.9) Exposed: 26 cases 49 controls	No association with glyphosate exposure and NHL	Vital status, age, state, smoking, family history, high risk occupation, high risk exposure. Not controlled for exposure to other pesticides.
De Roos *et al.* (2003) Iowa, Nebraska, Minnesota, Kansas, U.S.A.	Case-Control 1983-1986\Nebraska 1979-1981\Kansas 1979-1986 870 white male cases 2569 white male controls	Interview-based questionnaire, demographic	Logistic regression OR=2.1 (1.1-4.0) Exposed: 36 cases 61 controls Hierarchical regression OR=1.6; (0.9-2.8)	Significant increased OR in logistic model but in the hierarchical model, the OR attenuated and no significant association with glyphosate exposure and NHL	Age, study site, use of all other pesticides (group); hierarchal regression informed priors based on chemical-specific information
Lee *et al.* (2004a) Iowa, Nebraska, Minnesota, U.S.A	Population based Case-Control 1980-1986 872 white male cases	In person, structured interview (pesticide use, duration, frequency, first and last year used); 5-yr follow-up interview, 10-min telephone on pesticide use	Non-asthmatic OR=1.4 (0.98-2.1) (Exposed: 53 cases 91 controls) Asthmatic OR=1.2 (0.4-3.3) (Exposed: 6 cases 12 controls)	No significant association with glyphosate exposure and NHL either for asthmatics or non-asthmatics	Adjusted for age, vital status, state

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	OR=1.1 (0.7-1.9 (Exposed: 92 cases)	No significant association with glyphosate exposure and NHL	Age, smoking, other pesticides, alcohol consumption, family history of cancer, education
Hardell and Erickson (1999) Sweden	Population based Case-Control 1987-1990 404 male cases 741 male controls	Questionnaire and follow-up interview	Univariate OR=2.3 (0.4-13.0) (Exposed: 4 cases 3 controls) Multivariate OR=5.8 (0.6-54)	Some evidence of a link with glyphosate, matching variables; cannot conclude regarding causal role for any specific pesticide	Age, region, vital status (matching). Few subjects exposed. Variables used in multivariate were no specified. Study has limited power to detect an effect
Hardell *et al.* (2002) Sweden	Population based Case-Control Combined Hardell 1999 with another case-control study examining hairy cell leukemia (one of 61 types of NHL) 1987-1990 515 cases 1141 controls	Questionnaire and follow-up interview	Univariate OR=3.04 (1.08-8.52) (Exposed: 8 cases 8 controls) Multivariate OR=1.85 (0.55-6.20)	Risk attenuates when adjusted for other variables in the multivariate analysis	Age, country, study site, vital status, other pesticide exposure in the multivariate analysis

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Eriksson *et al.* (2008) Sweden	Population based Case-Control 1999-2002 910 cases 1016 controls	Questionnaire and follow-up interview	Univariate OR=2.02 (1.10-3.71) (Exposed: 29 cases 18 controls) Multivariate OR=1.55 (0.77-2.94) With <10 days/ year OR=1.69 (0.7-4.07) (Exposed: 12 cases 9 controls) With > 10 days/year OR=2.36 (1.04-5.37) (Exposed: 17 cases 9 controls) B-cell lymphoma OR=1.87 (0.998-3.51)	Suggestive association for NHL with glyphosate exposure	Age, sex, year of diagnosis. Multivariate analysis adjusted for exposure to other pesticides
McDuffie *et al.* (2001) Canada	Population based Case-Control 1991-1994 517 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	Univariate OR=1.26 (0.87-1.8) (Exposed: 51 cases 133 controls) Multivariate OR=1.20 (0.83-1.74)	No significant association with glyphosate exposure and NHL	Adjusted for statistically significantly medical variables (history of measles, mumps, cancer, allergy shots, and a positive family history of cancer) males only

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Hohenadel *et al.* (2011) Canada	Case-Control 1991-1994 513 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	OR=0.92 (0.54-1.55) (Exposed: 19 cases 78 controls)	No significant association with glyphosate exposure and NHL	Age, province and proxy respondent, males only
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.0 (0.5-2.2) (Exposed: 12 cases 24 controls)	No association with glyphosate exposure and NHL	Age, center, socioeconomic category
Cocco *et al.* (2013) Czech Republic, France, Germany, Italy, Ireland and Spain	EPICLYMPH Case-Control 1998–2003 2348 cases 2462 controls	Occupational exposure; trained interviewers conducted in person interviews with cases and controls	OR=3.1 (0.6-17.1) (Exposed: 4 cases 2 controls)	No significant association with glyphosate exposure and B-cell	Age, center, socioeconomic category
Hodgkin Lymphoma					
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.7 (0.6-5.0) (Exposed: 6 cases 15 controls)	No significant association with glyphosate exposure and HL	Age, center, socioeconomic category

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Karunanayake *et al.,* (2012). Canada	Case-Control 1991-1994 361 cases 1,506 controls	Questionnaire and follow-up interview	Univariate OR=1.14(0.74-1.76) (Exposed :38 133 controls) Multivariate OR=0.99 (0.62-1.56)	No association with glyphosate exposure and HL	History of measles, acne, hay fever, shingles and positive family history of cancer in a first-degree relative

D. Discussion

In epidemiologic studies, the quality of the exposure assessment is a major concern since the validity of the evaluations depends in large part on the ability to correctly quantify and classify an individual's exposure. During their life-time, farmers are typically exposed to multiple pesticides and several of them are used together posing a challenge for identifying specific risk factors. Moreover, there is no direct information on pesticide exposure or absorbed dose because analyses are based on self-reported pesticide use. The studies included in this epidemiology assessment relied primarily on questionnaires and interviews to describe participants' past and/or current exposure to glyphosate. Since the questionnaires are commonly used to account for exposure and capture self-reporting, it can be subject to misclassification and recall bias. For example, case-control studies are at risk of recall bias in the reporting of pesticide use in the past because cases may have spent more time thinking about past exposures than controls. This could lead to differential misclassification and bias relative risk from null. The possible effect of confounding factors, which are related to both the exposure of interest and the risk of disease, may make it difficult to interpret the results. Therefore, the ability of epidemiologic studies to provide convincing evidence of causation under such circumstances may be limited. Causation is suspected if several studies are consistent in their findings and; if the association between the agent and the risk of disease is strong (*i.e.*, high risk ratio). Support from animal data will help to make the case for causation, particularly by establishing biological plausibility and the existence of a potential mechanism. Another important consideration in assessing epidemiologic studies is that commercially formulated products (not the active ingredient) are used by farmers. For example, glyphosate is sold as Roundup®, which is a combination of the active ingredient and other chemicals that often include a surfactant (polyethyleneamine) used to enhance the spreading of spray droplets when they contact the foliage. Thus, it is possible that different glyphosate-containing formulations were used across the different studies.

Most of the studies discussed here were hypothesis-generating in nature, consisted of small sample sizes with limited power to detect associations and evaluated use of glyphosate in addition to several other pesticides and often evaluated risk of multiple different types of cancer. Therefore, the role of chance given the many different statistical tests performed and the lack of a pre-specified hypothesis, limit epidemiologic inference. This hypothesis-generating evidence observed in the studies requires further prospective follow-up studies to determine whether a true association with glyphosate is indeed null. The case-control studies are retrospective studies and are susceptible to recall bias for exposure reporting which could account for discrepancies in the study findings. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could also explain these inconsistencies in the data. In contrast, a prospective cohort study evaluates a number of diseases simultaneously and facilitates performance of periodic assessments of agricultural and other exposures. Periodic assessment of recent exposures enhances recall and reduces non-differential misclassification. The ability to determine exposure prior to the onset of a disease eliminates the case-recall bias, which was an issue identified as a weakness in case-control studies.

IV. EVALUATION OF CARCINOGENICITY IN ANIMALS

A total of 11 chronic toxicity/carcinogenicity studies (7 rat and 4 mouse) were included in this weight of evidence review. Of these, six studies were submitted for review to EPA under the registration/reregistration programs including two studies in rats (MRID No. 496311701 and 49704601) and one in mouse (MRID No. 49631702) not previously reviewed. Data for review of the other five studies were obtained from a published review article by Greim *et al.*, 2015 and were available online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423. The IARC acknowledged the Greim *et al.,* (2015) review article, but did not evaluate the studies cited in the review because the information provided in the review and its supplement was insufficient.

For this assessment, each study reported in the Greim *et al.,* (2015) review article was evaluated in accordance with the agency's 2012 Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf). In accordance with this guidance, the following four studies were not included in this weight of evidence assessment since there is low confidence were determined to be unreliable for carcinogenicity evaluation.

- A two year feeding study in Sprague-Dawley rats (Excel, 1997) was not included due to the lack of test article characterization (no purity of test material).

- The two-year drinking water study in Wistar rats reported by Chruscielska *et al.*, (2000) was not included since the tested material was a formulated product (13.6% ammonium salt) and there were a number of deficiencies (lack of purity, water consumption and body weight data) in the conduct and reporting of the study.

- An initiation-promotion study (George *et al.*, 2010) in male Swiss mice that tested a commercial formulation of glyphosate (41%) with study deficiencies (*e.g.* small number (20) of animals, tested only males, and lack of histopathological examination).

- A carcinogenicity study in Swiss mice (Feinchemie Schwebda, 2001) was not included due to the presence of viral infection within the colony, which confounded the interpretation of the study findings. Malignant lymphomas were reported in this study in all groups. However, lymphomas are one of the most common types of spontaneous neoplastic lesions in aging mice (Brayton *et al.*, 2012). Murine leukemia viruses (MuLVs) are a common cause of lymphoma in many different strains of mice (Ward 2006). Tadesse-Heath *et al.* (2000) reported 50% lymphoma (mostly B-cell origin) incidence in a colony of Swiss mice. Although the incidences in this study were within or near the normal variation of background occurrence, it is not clear whether or not the viral component may have contributed to incidence value reported or the lower survival seen at the high dose in the study. Raw data are not available to perform appropriate statistical analyses of the lymphomas correcting for the intercurrent mortality.

A. Carcinogenicity Studies in Rats

1. Lankas, G, P. A Lifetime Study of Glyphosate in Rats. December 23, 1981. Unpublished report No. 77-2062 prepared by Bio Dynamics, Inc. EPA Accession. No. 247617 – 247621. MRID No. 00093879.

a. Experimental Design

Groups of Sprague-Dawley rats (50/sex/dose) were fed diets containing glyphosate (98.7%, pure) at concentrations of 0, 30, 100 or 300 ppm for 26 months. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in females were maintained.

b. Survival Analysis

There were no treatment-related effects on survival at any dose level.

c. Discussion of Tumor Data

There was an increase in the incidences of interstitial cell tumors in the testes of male rats at the low (3/5; 6%), mid (1/50; 2%) and the high dose (6/50; 12%; P=0.013 pairwise comparison) when compared to controls (0/50; 0%). In 1991, HED's Cancer Peer Review Committee (CPRC) did not consider the increases to be treatment-related based on the following weight of evidence considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5%; range, 3.4% to 6.7%) and 5) no interstitial cell tumors were seen when tested at much higher doses in the same strain of rats in an another study (discussed below). The CARC agreed with the CPRC conclusion and rationale and noted additional rat studies which also showed no effect on interstitial cell tumors.

Although there was no evidence of a treatment-related increase in the incidences of pancreatic islet cell tumors in male rats, the data are presented in Table 4 since this tumor also seen in the second study discussed below.

Table 4. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats (MRID 00093879)				
Tumor Type	0 ppm	30 ppm	100 ppm	300 ppm
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Combined (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

d. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

The CPRC concluded that the highest dose tested was not adequate to assess the carcinogenic potential of glyphosate. Consequently, a second study was conducted (discussed below).

2. Stout, L. D. and Rueckerf, P.A. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; September, 26, 1990, MRID No. 41643801; Historical Controls; MRID No. 41728701.

a. Experimental Design

Groups of Sprague-Dawley rats (60/sex/dose) were fed diets containing glyphosate (96.5%, pure) at dietary concentrations of 0, 2000, 8000 or 20,000 ppm 24 months. These levels were equivalent to 0, 89, 362 or 940 mg/kg/day, respectively, for the males and 0, 113, 457 or 1183 mg/kg/day, respectively, for the females. An interim sacrifice was conducted on 10 rats/sex/dose at 12 months.

b. Discussion of Tumor Data

The most frequently seen tumors were pancreatic cell adenomas, hepatocellular adenomas and thyroid C-cell adenomas in males. Data for these tumors and the respective historical control data are presented in Tables 5 thru 11.

Pancreatic cell adenomas are presented in Table 5 and the historical control data are presented in Table 6. Hepatocellular adenomas seen in males are presented in Table 7 and the historical control data are presented in Table 8. The thyroid C-cell adenomas and/or carcinomas observed in males and females are presented in Tables 9 and 10, respectively, and the historical control data are presented in Table 11.

(i) Pancreas

There was no statistically significant trend test by dose for pancreatic islet cell tumors. Increased incidences of adenomas only were observed at the low- and high-dose groups but not at the mid-dose group.

Table 5. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas	1/43[a]	8/45	5/49	7/48[b]
(%)	(2)	(18)	(10)	(15)
P =	0.170	0.018*	0.135	0.042*
Carcinomas	1/43[c]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
P=	0.159	0.409	0.467	0.472
Combined	2/43	8/45	5/49	7/48
(%)	(2)	(18)	(10)	(15)
P=	0.241	0.052	0.275	0.108

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 81 in the 20,000 ppm group
c. First carcinoma observed at week 105 in the controls (0 ppm)
* Significant in a pair-wise comparison (P<0.05)

Historical control data on the incidence of pancreatic islet cell adenomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 6.

Table 6. Historical Control Data — Pancreatic Islet Cell Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)

Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Tumor Incidence	2/68	5/59	4/69	1/57	5/60	3/60	3/59
%	2.9%	8.5%	5.8%	1.8%	8.3%	5.0%	5.1%

The CPRC concluded that the pancreatic islet cell adenomas are not treatment-related based on the following weight of evidence considerations: 1) although the incidences at the low (18%) and high (15%) dose groups exceeded the historical control range (1.8–8.5%), there was lack of statistical significance in Cochran-Armitage trend test; 2) the tumor incidence in the concurrent control was at the low end of the historical control range; 3) considerable inter-group variability in the numbers of males with tumors (*i.e.*, no dose-response); 4) there were no preneoplastic changes; 5) there was no progression from adenomas to carcinomas; and 6) the apparent statistical significance of the pairwise comparisons of the treated groups with the concurrent control may be due to the low incidences in the controls and not to an actual carcinogenic response. Furthermore, the incidences of pancreatic cell tumors for the two studies did not show dose-response and the incidences were within the historical control range (0 to 17%) reported in the open literature (Arnold *et al.,* 1985; Borelli *et al.*, 1990; Borzelleca *et al.*, 1986, 1989, 1990; Burnett *et al.*, 1988; Trochimowicz *et al.*, 1988). The CARC agreed with the CPRC conclusion and rationale and noted subsequent rat studies which also showed no effect on islet cell tumors.

(ii) Liver

There was a dose trend for adenomas only. There were no statistically significant increases in the occurrence of benign or malignant hepatocellular tumor types (Table 7). The observed variations in incidence were within the range of the historical control data.

Table 7. Glyphosate: Hepatocellular Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/44[a] (5) 0.016*	2/45 (4) 0.683	3/49 (6) 0.551	7/48[b] (15) 0.101
Carcinomas (%) P =	3/44 (7) 0.324	2/45 (4) 0.489	1/49 (2) 0.269	2/48[c] (4) 0.458
Adenoma/Carcinoma (%) P =	5/44 (11) 0.073	4/45 (9) 0.486	4/49 (8) 0.431	9/48 (19) 0.245

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 88 in the 20000 ppm group
c. First carcinoma observed at week 85 in the 20000 ppm group

Historical control data on the incidence of hepatocellular adenomas and carcinomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 8.

Table 8. Historical Control Data : Hepatocellular Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)							
Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Adenomas	5/60 (8.3%)	11/68 16.2%)	1/70 (1.4%)	3/59 (5.1%)	11/60 (18.3%)	5/60 8.3%)	4/60 (6.7%)
Carcinomas	4/60 (6.7%)	0/68 (0%)	1/70 (1.4%)	2/59 (3.4%)	3/60 (5%)	1/60 (1.7%)	0/60 (0%)

The CPRC concluded that the slightly increased incidence of adenomas in male rats are not treatment-related since: 1) the increase was not statistically significant in pairwise comparison with the controls; 2) the incidences were within the historical control range; 3) except for a single animal at the mid-dose late in the study (89 weeks), no hyperplasia, preneoplastic foci or other non-neoplastic lesions were seen; and 4) there was no evidence of progression from adenomas to carcinomas. The CARC agreed with the CPRC conclusion and rationale.

(iii) Thyroid

The increased incidences in C-cell adenomas observed at the mid and high-dose groups of rats of both sexes did not show a statistically significant difference in pairwise comparisons with the controls (Table 9 and 10, respectively). There was a dose trend observed for adenomas and adenomas/carcinomas in females (P=0.03). Historical control data are presented in Table 11.

Table 9. Glyphosate: Thyroid C-Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/54[a, b] (4) 0.069	4/55 (7) 0.348	8/58 (14) 0.060	7/58 (12) 0.099
Carcinomas (%) p =	0/54 (0) 0.452	2/55[c] (4) 0.252	0/58 (0) 1.000	1/58 (4) 0.518
Adenoma/Carcinoma (%) p =	2/54 (11) 0.077	6/55 (11) 0.141	8/58 (14) 0.060	8/58 (14) 0.060

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 54 in the controls
c. First carcinoma observed at week 93 in the 20,000 ppm

Table 10. Glyphosate: Thyroid C-Cell Tumors in Female Sprague Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P=	2/57[a] (4) 0.031*	2/60 (7) 0.671	6/59[b] (10) 0.147	6/55 (11) 0.124
Carcinomas (%) P=	0/57 (0) 0.445	0/60 (0) 1.000	1/59[c] (2) 0.509	0/55 (0) 1.000
Adenoma/Carcinoma (%) p=	2/57 (4) 0.033*	2/60 (3) 0.671	7/59 (12) 0.090	6/55 (11) 0.124

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 72 in the controls
c. First carcinoma observed at week 93 in the 8000 ppm group.

Table 11. Historical Control Data – Thyroid C-cell Tumors in Sprague-Dawley Rats (MRID No. 41728701)		
Tumor Type	Males	Females
Adenomas	1.8 – 10.6%	3.3 – 10.0%
Carcinomas	0.0 – 5.2%	0.0 – 2.9%

The CPRC concluded that the thyroid tumors in either sex are not treatment-related since: 1) the increased incidences exhibited no statistically significant trend or pairwise comparisons with the controls in males; 2) in females, there was a trend but no pairwise significance; 3) there was no progression from adenomas to carcinomas; and 4) there was no dose-related increase in severity of grade or incidence of hyperplasia in males or females. The CARC agreed with the CPRC conclusion and rationale and noted other rat studies which showed no effect on thyroid C-cell tumors.

c. Non-Neoplastic Lesions

There were no treatment-related precursor lesions at any dose level.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was near or beyond the limit dose (1000 mg/kg/day).

3. **Atkinson, C., Strutt, A., Henderson, W., et al. (1993). 104-Week chronic feeding/ oncogenicity study in rats with 52-week interim kill. Inveresk Research International (IRI), Tranent, Scotland. Study No. 438623; IRI Report No. 7867. April 7, 1993. MRID No. 49631701. Unpublished.**

a. Experimental Design

In a combined chronic toxicity/carcinogenicity study, glyphosate (98.9% pure) was administered to 50 male and female Sprague-Dawley rats/sex/dose in the diet at 0, 10, 100, 300, and 1000 mg/kg/day for 104 weeks. An interim sacrifice was conducted on 15 rats/sex/dose after 52 weeks of treatment.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

There were no treatment-related increases in the occurrence of any tumor type in this study.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was the limit dose (1000 mg/kg/day) and at this dose increased salivary gland weight accompanied by cellular alterations in the mandibular and/or parotid glands occurred in both males and females.

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4. **Brammer. (2001). Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Rats. Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK: Syngenta. (MRID No. 49704601).**

a. Experimental Design

In a combined chronic toxicity study, glyphosate acid (97.6% pure) was administered to groups of Wistar rats in the diet. Groups of 52 male and 52 female rats received diets containing 0, 2,000, 6,000, and 20,000 ppm glyphosate for 24 months. The achieved doses were 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437 or 1498 mg/kg/day in females, respectively. Three satellite groups of 12 rats/sex/group were also included for

interim sacrifice at 12 months of treatment. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

As shown in Table 12, there was an increase in the incidence of hepatocellular adenomas in male rats at the high dose when compared to controls. This increase was not considered to be treatment-related due to 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the range (0–11.5%) of historical controls for this strain (Wistar) of rats in 26 studies conducted during the relevant time period (1984–2003) at the testing laboratory; and 5) the 0% incidence in concurrent controls is lower than the average background incidence for liver adenomas in male Wistar rats.

Table 12. Liver Adenomas in Male Wistar Rats Fisher's Exact Test and Exact Trend Test Results

	0	2000	6000	20000
Adenomas	0/52[a]	2/52	0/52	5/52
(%)	(0)	(4)	(0)	(10)
P =	0.00804**	0.24757	1.00000	0.02826*

a =Number of tumor-bearing animals/Number of animals examined.

In addition, statistically higher survival (P=0.02) was observed in males at 20,000 ppm at the end of 104 weeks relative to controls, and an overall trend for improved survival was observed in treated males (P=0.03). The inter-current (early) deaths were 37/52, 36/52, 35/52, and 26/52 for the control, low, mid and high dose groups, respectively. The terminal deaths were 16/52, 17/52, 18/52, and 26/52 for the control, low, mid and high dose groups, respectively. This survival bias in the high dose group could easily explain a modestly higher incidence of an age-related background tumor like liver adenoma (and fits with lack of associated lesions). In the 1990 study in Sprague-Dawley rats (MRID No. 41643801) there was also a weak but significant trend test for liver adenomas in males (P=0.02, no pairwise); however, in that study adenomas in all treatment groups were still within the historical control and the CPRC concluded that this effect was not treatment-related, as discussed above. The lack of increased liver tumor incidence in the other rat studies provide additional evidence for lack of an actual carcinogenic response in the liver.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in any organs of either sex at any dose level tested.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes (1214 mg/kg/day in males and 1498 mg/kg/day in females) exceeded the limit dose (1000 mg/kg/day). Treatment-related findings at these doses were observed in the liver and kidney, notably renal papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, hematuria and slight increases in the incidence of proliferative cholangitis and hepatitis.

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5. Feinchemie Schwebda. (1996). Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats. Bangalore, India: Rallis India, Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (96.0-96.8% pure) was administered to groups of Wistar rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 100, 1000, and 10000 ppm glyphosate for 24 months. The average achieved doses were 0, 7.4, 73.9, and 740.6 mg/kg/day. Parameters evaluated included clinical signs, body weights, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy, and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no non-neoplastic lesions at any dose level in either sex.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The doses tested were determined to be adequate in both sexes since the highest dose tested (741 mg/kg/day) approached the limit dose (1000 mg/kg/day).

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6. Arysta Life Sciences. (1997a). HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (94.6–97.6% pure) was administered to groups of Sprague-Dawley rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 3000, 10000, or 30000 ppm glyphosate for 24 months. The achieved doses were 0, 104, 354 or 1127 mg/kg/day in males and 0, 115, 393, or 1247 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose 10,000 ppm (1127 mg/kg/day in males and 1247 mg/kg/day in females) exceed the limit dose (1000 mg/kg/day) and there were increased cecum weights, distension of the cecum, loose stool, follicular hyperkeratosis and/or folliculitis/follicular abscess of the skin, and decreased body weights.

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7. **Nufarm. (2009a). Glyphosate Technical: Dietary Combined Chronic Toxicity/ Carcinogenicity in the Rat. Shardlow, Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015)**.

a. Experimental Design

In a combined chronic toxicity study, glyphosate (95.7% pure) was administered to groups of Wistar rats in the diet. Groups of 51 rats/sex/group received diets containing 0, 1500, 5000, and 15,000 ppm glyphosate for 24 months. To ensure that a received limit dose of 1000 mg/kg/day was achieved, the highest dose level was progressively increased to 24000 ppm. The achieved doses were 0, 86, 285 or 1077 mg/kg/day in males and 0, 105, 349 or 1382 mg/kg/day, in females. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in either sex at any dose level.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest doses 1077 mg/kg/day in males and 1382 mg/kg/day in females exceed the limit dose (1000 mg/kg/day).

B. Carcinogenicity Studies in Mice

1. Knezevich, A.L and Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamic Inc., dated July 21, 1983. Report No. 77-2011. EPA Accession No. 251007 – 251009, and 251014.

a. Experimental Design

In a carcinogenicity study, groups of 50 male and female CD-1 mice received glyphosate (99.78%, pure) at dietary levels of 0, 1000, 5000, or 30,000 ppm for two years. These doses were equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, and histopathological examination.

b. Discussion of Tumor Data

The incidences of renal tubule adenomas were as follows: 0/49 in the controls; 0/49 at the low-dose; 1/50 at the mid-dose; and 3/50 at the high dose (TXR No. 0004370).

In 1985, the Registrant directed a re-evaluation of the original renal section by a consulting pathologist (Dr. Marvin Kuschner). This evaluation identified a small renal tubule adenoma in one control male mouse (animal number 1028) which was not diagnosed as such in the original pathology report (TXR No. 0004855).

In 1986, at the request of the agency, additional renal sections (3 sections/kidney/mouse spaced at 150 micron intervals) were evaluated in all control and all glyphosate-treated male mice in order to determine if additional tumors were present. The additional pathological and statistical evaluations concluded that the renal tumors in male mice were not compound-related (TXR No. 0005590).

At the request of the agency, the Pathology Work Group (PWG) examined all sections of the kidneys including the additional renal sections. The renal tubular-cell lesions diagnosed by the PWG are presented below in Table 13. The PWG noted that because differentiation between tubular-cell adenoma and tubular-cell carcinoma is not always clearly apparent and because both lesions are derived from the same cell type, it appropriate to combine the incidences for purposes of evaluation of statistical analysis. Statistical analyses are presented in Table 14. The PWG unanimously concluded that these lesions are not compound-related based on the following considerations: 1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the controls and there was no evidence of a significant linear trend; 3) multiple renal tumors were not found in any animal; and 4) compound-related nephrotoxic lesions,

including pre-neoplastic changes, were not present in male mice in this study (TXR No. 0005590).

Table 13. Glyphosate: Kidney Tumor in Male CD-1 Mice — PWG				
Dose/Tumor Type	Control	1000 ppm	5000 ppm	30,000 ppm
	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Tubular-cell adenoma	1/49	0/50	0/50	1/50
Tubular-cell carcinoma	0	0/50	1/50	2/50
Combined incidence	1/49 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)

Statistical analysis of the male mouse renal tumors diagnosed by the PWG are presented below in Table 14.

Table 14. Kidney Tumors in Male CD-1 Mice — PWG Cochran-Armitage Trend & Fisher's Exact Test (MRID 00130406)				
Tumor Type	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Adenomas (%) P =	1/49 (2) 0.4422	0/49 (0) 1.0000	0/50 (0) 1.00000	1/45 (2) 0.7576
Carcinomas (%) P =	0/49 (0) 0.0635	0/49 (0) 1.0000	1/50 (2) 0.5051	2/50 (4) 0.2525
Combined (%) P =	1/49 (2) 0.0648	0/49 (0) 1.0000	1/50 (2) 0.7576	3/50 (6) 0.3163

Historical control data from the testing laboratory (Bio-dynamics) during the glyphosate-study period (1976-1982) are presented in Table 15.

Table 15. Historical Control Data- Kidney tumors in CD-1 Mice — Bi/dynamics Inc.														
Study I.D	A		B		C		D		E		F		G	
Study Period	6/78 - 7/80		12/77- 4/80		12/77- 3/80		10/78- 4/81		11/78- 4/81		11/77- 4/80		10/77-4/80	
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
Tubular Adenoma		1	0	0	0	0	0	0	0	2	0	0	0	0

Historical control data from 14 studies conducted between 1977 and 1981 at the testing laboratory indicated that the mouse renal tumors ranged from 0 to 3.3% and the incidence in the current study (3/50; 6%) exceeded the upper limit of the historical control range (TXR No. 0007252).

The CPRC determined that glyphosate produced an equivocal carcinogenic response in male mice characterized by an increased incidence of renal tubular neoplasms. The biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls for adenomas, carcinomas and the combined tumors; b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (*e.g.* tubular necrosis/regeneration, hyperplasia, hypertrophy, etc.), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males; e) although the incidences exceeded the historical control, this finding did not override the lack of statistical significance of comparison to the concurrent controls. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not consider the renal tumors to be treatment-related. The CARC reaffirmed the CPRC conclusion and rationale. Also, the lack of increased renal tumors in the other mouse studies in the same strain provides additional evidence for lack of an actual carcinogenic response in the kidneys.

c. Non-Neoplastic Lesions

The incidence of centrilobular hepatocyte hypertrophy was slightly but not significantly increased in high-dose male mice at terminal sacrifice if all mice were included in the analyses. Centrilobular hepatocyte necrosis was significantly ($P \leq 0.01$) increased in high-dose male mice (10/50; 20%) compared to controls (2/49; 4%). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice. There was a dose-dependent increase in the proximal tubular epithelial basophilia in female mice; the incidences were: 0/50 (0%) in the controls, 2/50 (4%) at the low dose, 4/50 (8%) at the mid dose, and 9/50 (18%) at the high dose ($P \leq 0.01$). All other tissue alterations occurred sporadically and were found with approximately equal frequency and severity in control and treated animals. These were considered unrelated to glyphosate treatment.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The high dose tested in males (4945 mg/kg/day) and females (6069 mg/kg/day) was approximately 4 to 6-fold higher than the limit dose (1000 mg/kg/day), which produced highly significant reduction in body weights in both sexes. Therefore, the doses tested were determined to be adequate to assess the carcinogenic potential of glyphosate in this study.

2. Atkinson, C., Martin, T., Hudson, P., and Robb, D. (1993). Glyphosate: 104 week dietary carcinogenicity study in mice. Inveresk Research International, Tranent, EH33 2NE, Scotland. IRI Project No. 438618. April 7, 1993. MRID 49631702.

a. Experimental Design

In a carcinogenicity study, glyphosate (97.5 – 100.2% pure) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. No interim sacrifices were performed. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, necropsy and histopathological examination.

b. Discussion of Tumor Data

As shown in Table 16, hemangiosarcomas were found in 4/45 (9%) high-dose male mice compared to none in the controls. In the treated mice at the high dose, one had the tumors present in the liver and spleen, one had the tumor present in the liver only, one had the tumors present in the liver, spleen, and prostate, and one had the tumor present in the spleen only. No hemangiosarcomas were found in the control or low- and mid-dose mice.

Table 16. Hemangiosarcomas in Male CD-1 Mice Fisher's Exact Test and Exact Trend Test Results

Dose (mg/kg/day)	0	100	300	1000
Hemangiosarcomas	0/47[a]	0/46	0/50	4/45
(%)	(0)	(0)	(0)	(9)
P =	0.00296**	1.00000	1.00000	0.05332

a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in hemangiosarcomas in male mice was not considered to be treatment-related due to 1) tumors seen only at the limit dose; 2) absence of statistical significance in the pairwise analysis; 3) the incidences was near or the same as the upper limit (0–8%) for the performing laboratory; 4) hemangiosarcomas were not seen in male mice in the other three studies when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4348–5874 mg/kg/day) in this strain of mouse; 6) the considerable inter-group variability in the number of female mice with this tumor (0, 2 , 0 and 1 in the control, low-, mid- and high-dose groups, respectively); 7) Hemangiosarcomas are commonly observed in mice as both spontaneous and treatment-related tumors arising from endothelial cells; 8) hemangiosarcomas appear in both sexes but are generally more common in males (CD-1); 9) As vascular tumors, they can occur at different sites but liver and spleen tend to be the most common sites in male mice.

c. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose tested was the limit dose (1000 mg/kg/day).

3. **Arysta Life Sciences. (1997b). HR-001: 18-Month Oncogenicity Study in Mice. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015)**.

a. Experimental Design

In a carcinogenicity study, groups of ICR-CD-1 mice (50/sex/group received diets containing glyphosate (94.6–97.6% pure) at 0, 1600, 8000 or 40,000 ppm for 18 months. The achieved doses were 0, 165, 838 or 4348 mg/kg/day in males and 0, 153, 787 or 4116 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes exceeded (4-fold) the limit dose (1000 mg/kg/day).

4. Nufarm. (2009b). Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In another feeding study, CD-1 mice (50/sex/dose) received glyphosate (94.6–97.6%, pure) at 0, 500, 1500, or 5000 ppm for 18 months. The calculated test substance intake was 0, 85, 267 or 946 mg/kg/day. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, gross necropsy and histopathological examination.

b. Discussion of Tumor Data

In male mice at the high dose (5000 ppm) there were increases in the incidences of adenocarcinomas of the lung and malignant lymphomas as shown in Tables 17. For the lung adenocarcinomas, the increases did not reach statistically significant pairwise differences, although the trend was significant. For the malignant lymphomas there was a trend and pairwise significance. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

Table 17. Lung Adenocarcinomas and Malignant Lymphomas in Male CD-1 Mice (Greim *et al.*, 2015)
Fisher's Exact Test and Exact Trend Test Results

Dose (ppm)	0	500	1500	5000
Lung Adenocarcinoma	5/51[a]	5/51	7/51	11/51
(%)	(10)	(10)	(14)	(22)
P =	0.02906**	0.62953	0.37996	0.08609
Malignant Lymphoma	0/51	1/51	2/51	5/51
(%)	(0)	(2)	(4)	(10)
P =	0.006633**	0.50000	0.24752	0.02820*

a= Number of tumor bearing animals/Number of animals examined.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in lung adenocarcinomas was not considered to be treatment-related due to: 1) absence of statistical significance in the pairwise analysis; 2) the incidences in all treatment groups including the controls were within the historical control range (1.43–26%) for the performing laboratory; and 3) lung tumors were not seen in the other three studies when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

Historical control data and results from the 5 studies can be used to put this finding into perspective. The malignant lymphomas were not considered to be treatment-related since the 0% incidence of this lesion in the concurrent control for male mice was lower than the historical control mean (4.5%) and range (1.5–21.7%) in this strain and age of mice (Gikins and Clifford, 2005; Son and Gopinath, 2004). Therefore, the apparent statistical significance of the pairwise comparisons of the high dose male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response. In addition, malignant lymphomas were not seen in the other three studies in this strain of mice when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

c. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose (947 mg/kg/day) tested approached the limit dose (1000 mg/kg/day).

IV. TOXICOLOGY

A. Metabolism

Single or repeated doses of radiolabeled ^{14}C-glyphosate were administered orally to male and female Sprague-Dawley rats. Following a single oral dose of, ^{14}C-glyphosate, 30 to 36% of the dose was absorbed and less than 0.27% of the dose was eliminated as CO_2. 97.5% of the administered dose was excreted in the urine and feces as the parent compound, glyphosate. Amino methyl phosphonic acid (AMPA) was the only metabolite found in urine (0.2–0.3% of the administered dose) and feces (0.2–0.4% of the administered dose). Less than 1.0% of the absorbed dose remained in tissues and organs, primarily in bone tissue. Repeated dosing at 10 mg/kg did not significantly change the metabolism, distribution or excretion of glyphosate.

In a second study, male and female Sprague-Dawley rats received single intraperitoneal injections of radiolabeled ^{14}C-glyphosate at 1150 mg/kg. Blood samples were collected 0.25, 0.50, 1, 2, 4, 6 and 10 hours after injection. Femoral bone marrow samples were collected from one third of the male and female rats sacrificed at 0.5, 4, or 10 hours after injection. Thirty minutes after injection of glyphosate, the concentration of radioactivity in the bone marrow of male and female rats was equivalent to 0.0044% and 0.0072%, respectively, of the administered dose. Assuming first order kinetics, the decrease in radioactivity in bone marrow occurred with a half-life of 7.6 and 4.2 hours for males and females, respectively. Similarly, the half-lives of the radioactivity in plasma were approximately 1 hour for both sexes. These findings indicate that very little glyphosate reaches bone marrow, that it is rapidly eliminated from bone marrow, and that it is even more rapidly eliminated from plasma.

B. Mutagenicity

In 1991, the Carcinogenicity Peer Review Committee concluded that there was no evidence of genotoxicity for glyphosate based on negative findings in submitted guideline studies for the bacterial reverse mutation test (MRID 00078620), *in vitro* mammalian cell gene mutation test in CHO cells (MRID 00132681), *in vivo* mammalian bone marrow chromosomal aberration test (MRID 00132683) and a "rec assay" used to detect DNA-damaging agents in *Bacillus subtilis* (MRID 00078619) (TXR 0008898).

Glyphosate has also been evaluated for its genotoxic potential in other regulatory and published literature studies. Extensive reviews of the available genotoxicity studies for glyphosate and glyphosate products were conducted by Williams *et al.* (2000) and by Kier and Kirkland (2013). IARC also conducted a review of the publically available genetic toxicity data for glyphosate and glyphosate-based formulations (IARC, 2015).

Williams *et al.*, (2000) concluded that "glyphosate is neither mutagenic nor clastogenic." Similarly, Kier and Kirkland (2013) concluded a "lack of genotoxic potential for both glyphosate and glyphosate based formulations (GBFs) in core gene mutation and chromosomal effect endpoints." Kier and Kirkland (2013) also stated that "the observations of DNA-damage effects seems likely to be secondary to cytotoxic effects." However, IARC (2015) concluded that "there is strong evidence that glyphosate causes genotoxicity." It should be noted that the IARC's conclusion was based not only on studies conducted with the active ingredient but also on studies conducted with the formulation products such as Roundup. Roundup is a combination of the active ingredient and other chemicals, including a surfactant (polyoxyethyleneamine) which enhances the spreading of spray droplets when contact foliage. Of note, the review article by Kier and Kirkland (2013) and supplemental information provided on the publisher's website were not considered in the IARC evaluation.

In this assessment, the CARC considered a total of 54 studies including those submitted to the agency under 40 CFR Part 158 as well as the studies presented in the review articles by Williams *et al.* (2000), Kier and Kirkland (2013), and the IARC monograph (2015). Consistent with OPP's Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf), literature studies discussed in the reviews such as IARC that did not meet the Klimisch criteria for reliability (*e.g.* lack of adequate glyphosate purity information for the test material) were not considered by the CARC. The CARC determined the mutagenic potential of glyphosate in humans by conducting a weight-of-evidence evaluation of the results from the cited bacterial reversion (Ames) assays, *in vitro* mammalian gene mutation assays, *in vitro* and *in vivo* chromosomal aberration and micronucleus assays as well as other relevant assays evaluating DNA damage.

1. Bacterial reverse mutation assays

As shown in Table 18, glyphosate was not mutagenic in any of the *in vitro* bacterial mutation assays using *S. typhimurium* or *E. coli* tester strains with or without microsomal S9 metabolic activation. These results are consistent with the negative findings in the previously reviewed EPA guideline (870.5100) bacterial reverse gene mutation study (MRID 00078620).

Table 18. Results from Bacterial Reverse Gene Mutation Assays[1]

Author	Cell/Strain[2]	Purity	Highest test concentration	Results –S9	Results +S9
Akanuma,M. (1995)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.7%[3]	5000 µg/plate	Negative	Negative
Callander, R.D. (1996)	TA98, TA100, TA1535, TA1537; WP2P and WP2*uvr*A	95.6%[3]	5000 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	76.1%[4]	100 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	96.4%	3160 µg/plate	Negative	Negative
Flügge, C. (2009)	TA98, TA100, TA102, TA1535, TA1537	98.8%	3160 µg/plate	Negative	Negative
Jensen, J.C. (1991)	TA98, TA100, TA1535, TA1537	98.6%	2500 µg /plate w/o S9; 5000 µg /plate w/ S9	Negative	Negative
Li and Long (1988)	TA98, TA100, TA1535, TA1537, TA1538;	98%	5000 µg/plate	Negative	Negative
NTP (1992)	TA97, TA100, TA1535	98%	10,000 µg /plate	Negative	Negative
Schreib, G. (2010)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96%	5000 µg/plate	Negative	Negative
Shirasu et al. (1978)	TA98, TA100, TA1535, TA1537, TA1538 and WP2*uvr*A	98.4%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007c)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.0%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007a)	TA98, TA100, TA1535, TA1537; WP2uvrA	95.1%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009b)	TA98, TA100, TA1535, TA1537;WP2P and WP2*uvr*A	96.3%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009a)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96.66%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007b)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	97.7%	5000 µg/plate	Negative	Negative
Suresh, T.P. (1993)	TA98, TA100, TA1535, TA1537, TA1538	96.0%	1000 µg/plate	Negative	Negative
Thompson, P.W. (1996)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.3%	5000 µg/plate	Negative	Negative

1. Studies cited in Williams *et al*. (2000), Kier and Kirkland (2013), or IARC monograph.
2. *S. typhimurium* strains (TA97, TA98, TA100, TA102, TA1535, TA1537, and/or TA1538) or *E. coli* strains (WP2P and WP2*uvr*A)
3. Glyphosate acid
4. Monoammonium glyphosate salt

2. *In vitro* mammalian cell gene mutation assays

Glyphosate did not induce forward mutations in mouse lymphomas cells or Chinese hamster ovary (CHO) cells in the presence or absence of metabolic (S9) activation (Table 19).

Table 19. Results from mammalian gene mutation assays[1].

Author	Assay Type	Cell type	Purity	Highest conc.	Result -S9	Result +S9
Clay (1996)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	95.6%	1.0 mg/mL	Negative	Negative
Jensen, J.C. (1991)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	98.6%	5.0 mg/mL	Negative	Negative
Li and Long (1988)	*In vitro* mammalian gene mutation	CHO cells/ HGPRT locus	98%	22.5 mg/mL	Negative	Negative

1. Studies cited in Williams's *et al.* (2000), Kier and Kirkland (2013), or IARC monograph.

3. *In vitro* chromosomal aberration assays

Lioi *et al.* (1998a, 1998b) reported positive findings for chromosomal aberrations in human and bovine lymphocytes treated with glyphosate *in vitro* in the absence of S9 activity. As discussed in the Williams review, there is less confidence in the Lioi *et al.* results based on the use of an unusual 72-hour treatment protocol and the observation of reduced cell growth in glyphosate-exposed cells (an indication of a toxic effect) which can affect the evaluation of the study. Lioi *et al.* also reported chromosomal damage in lymphocytes treated with other known non-genotoxic pesticides in this study at concentration ranges similar to where they reported effects for glyphosate. By contrast, when the tests were performed according to the OECD guideline, Van de Waart (1995) reported no significant increase in chromosomal aberrations in human lymphocytes treated with up to 0.56 mg/mL (-S9) and 0.33 mg/mL (+S9) glyphosate, which are concentrations 3 orders of magnitude higher than those at which Lioi *et al.* reported aberrations. Glyphosate was negative in two other *in vitro* chromosomal aberrations studies using human lymphocytes (Fox, 1998; Manas *et al.* 2009) and did not induce chromosomal aberrations in Chinese hamster lung cells (Matsumoto, 1995; Wright, 1996). A summary of the findings is presented in Table 20.

Table 20. Results from *in vitro* chromosomal aberration assays[1].

Authors	Assay	Cell type	Purity	Highest test concentration	Result -S9	Result +S9
Van de Waart (1995)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	0.56 mg/mL with S9; 0.33 mg/mL w/o S9	Negative	Negative
Fox, V. (1998)	Chromosome Aberration	Human peripheral lymphocytes	95.6%[2]	1250 ug/mL	Negative	Negative
Lioi et al. (1998a)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	1.4 mg/L	Positive	Not Tested
Manas et al. (2009)	Chromosomal Aberration	Human peripheral lymphocytes	96%	6 mM	Negative	Not Tested
Lioi et al. (1998b)	Chromosomal Aberration	Bovine peripheral lymphocytes	>98%	2.9 mg/L	Positive	Not Tested
Matsumoto, K. (1995)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.68%[2]	1000 ug/mL	Negative	Negative
Wright, N.P. (1996)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.3%	1250 ug/mL	Negative	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

4. *In vivo* micronucleus and chromosomal aberration assays

Numerous studies were evaluated to determine the potential for glyphosate to induce micronuclei in rodent bone marrow cells. Studies included both intraperitoneal (IP) and oral routes of glyphosate administration. In a literature study by Bolognesi *et al.* (1997), the authors reported an induction of micronuclei in male mice treated with up to 300 mg/kg (injected as two ½ doses). It is noted that this study included only 3 animals/dose, rather than the 5 animals/dose recommended in the agency's test guideline (870.5395). In another literature study, Manas *et al.* (2009) reported an induction of micronuclei in BALB/C mice when tested up to 200 mg/kg glyphosate. However, there is some concern regarding how the micronuclei were scored in this study. As stated in the Kier and Kirkland review, Manas *et al.* (2009) reported their findings as an increase in micronucleated erythrocytes rather than polychromatic erythrocytes. Scoring all erythrocytes rather than immature polychromatic erythrocytes can impact the interpretation of the study as the effects cannot be solely attributed to treatment by the test article. Suresh *et al.* (1993) reported an increase in micronuclei in females only in Swiss albino mice treated with 5 mg/kg glyphosate; however, this occurred at a dose that is more than twice the limit dose for the agency's guideline study. Although the above authors reported positive findings, a vast majority of the *in vivo* genotoxicity studies (including the previously reviewed guideline mammalian bone marrow chromosomal aberration test) were negative at doses similar to or higher than the studies discussed above, regardless of the dosing regimen or route of administration. Furthermore, glyphosate was also negative in two rodent dominant lethal tests. A summary of the findings are reported in Table 21.

Table 21. Results from *in vivo* genotoxicity assays[1].

Author	Assay Type	Species/strain	Purity	Highest conc.	Results	Comments
Bolognesi *et al.* (1997)	Micronucleus test	Male mice (strain not provided)	99.9%	300 mg/kg	Positive	Two IP injections of ½ dose; 3 mice/dose
Durward, R. (2006)	Micronucleus test	Young adult male and female albino Crl:CD-1TM(ICR)BR mice	95.7%	600 mg/kg	Negative	Single IP injection; Significant increase in % PCEs per 1000 erythrocytes was observed in the 24-hour; however not 48-hour at 600 mg/kg
Flügge, C. (2009)	Micronucleus test	Male and female CD rats	98.8%	2000 mg/kg	Negative	Single dose; oral gavage
Fox and Mackay (1996)	Micronucleus test	Male and female CD-1 BR mice	95.6%[2]	5000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2005)	Micronucleus test	Male and female NMRI mice	97.73%	2000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2008)	Micronucleus test	NMRI male mice	99.1%	2000 mg/kg	Negative	Single dose; oral gavage
Jensen, J.C. (1991)	Micronucleus test	Young adult male and female NMRI SPF mice	98.6%	5000 mg/kg	Negative	Single dose; oral gavage
Manas *et al.* (2009)	Micronucleus	BALB/C mice	96%	200 mg/kg	Positive	Two IP doses, 1 day apart
NTP (1992)	Micronucleus test	Male and female B6C3F1 mice	99%	11,379 mg/kg/day	Negative	Dietary admin., 13 weeks
Suresh, T.P. (1993)	Micronucleus test	Young Swiss albino male and female mice	98.6%	5000 mg/kg	Males: Negative Females: Positive	Two doses 1 day apart; oral gavage
Suresh, T.P. (1994)	Mouse Bone Marrow Chromosome Aberration	Male and female Swiss albino mice	96.8%	5000 mg/kg	Negative	Two doses, 24 hours apart; oral gavage
Suresh, T.P. (1992)	Rodent dominant lethal test	Male and female Wistar rats	96.8%	500 mg/kg (single dose); 100 mg/kg (5 daily doses)	Negative	
Wrenn (1980)	Rodent dominant lethal test	Mouse; gavage	98.7%	2000 mg/kg	Negative	

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid
3. IP= intraperitoneal injection

5. Other genotoxicity assays

Inconsistent responses were reported in a number of assays designed to detect DNA damage, including sister chromatid exchange (SCE) assay, unscheduled DNA synthesis assay, and the comet assay (also known as the single cell electrophoresis assay). Positive responses in these assays do not necessarily indicate a chemical is DNA-reactive (*i.e.* mutagenic), but rather that DNA damage occurred under conditions of the assay. Glyphosate was also negative in two Rec-DNA repair tests in *B. subtilis*. The results of these genotoxicity studies are presented in Table 22.

Table 22. Additional genotoxicity assays of glyphosate

Authors	Assay Type	Cell Type	Purity	Highest test conc.	Results
Bolognesi *et al.* (1997)	Sister chromatid exchange (SCE)	Human peripheral blood (*in vitro*)	99.9%	1000 ug/mL	Positive
Lioi *et al.* (1998a)	SCE	Human peripheral blood (*in vitro*)	>98%	1.4 mg/L	Equivocal
Lioi *et al.* (1998b)	SCE	Bovine peripheral blood (*in vitro*)	>98%	2.9 mg/L	Equivocal
Li and Long (1988)	Unscheduled DNA synthesis (UDS)	Rat hepatocytes (*in vitro* exposure)	98%	0.125 mg/mL	Negative
Rossberger,(1994)	UDS	Primary rat hepatocytes	98%	111.69 mM	Negative
Bolognesi *et al.* (1997)	DNA Damage /reactivity/UDS	Mouse; IP administration	99.9%	300 mg/kg	Equivocal
Bolognesi *et al.* (1997)	DNA Damage/reactivity/UDS	Mouse; IP; alkaline solution of extracted DNA	99.9%	300 mg/kg	Positive
Alvarez-Moya et al. (2014)	Comet assay	Human lymphocytes	96%[2]	700 µM	Positive
Lueken *et al.* (2004)	Comet assay	Human fibroblasts GM 5757	98.4%	75 mM	Negative
Manas *et al.*(2009)	Comet assay	Liver Hep-2 cells	96%	7.5 mM	Positive
Mladinic et al. (2009)	Comet assay	Human lymphocytes	98%	580 ug/mL (toxic); approximately 3.43 mM	Positive
Rossberger, S. (1994)	DNA repair test	Male SD rat primary hepatocytes	>98%	111.69 mM	Negative
Akanuma, M. (1995)	DNA repair test (Rec- assay)	*Bacillus subtilis* M45 rec-/ H17 rec+	95.68%[2]	240 ug/disk	Negative
Li and Long (1988)	DNA repair test (Rec assay)	*B. subtilis* H17, rec+; M45, rec-	98%	2 mg/disk	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

6. Conclusions

In summary, glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronuclei or chromosomal aberration studies considered in this assessment by the CARC. Some positive results were reported in SCE and comet assays in the open literature; however, there is no convincing evidence that the DNA damage is a direct effect of glyphosate exposure, but rather may be secondary to cytotoxicity or oxidative damage.

C. Structure-Activity Relationship

At present there are no structurally related pesticides registered by the agency which resemble glyphosate. Sulfosate, the trimethylsulfonium salt of glyphosate (also known as glyphosate-trimesium) is a 1:1 molar salt of N-(phosphonomethyl) glycine anion (PMG) and the trimethylsulfonium cation (TMS). Sulfosate was evaluated for its carcinogenic potential following dietary administration to male and female mice at 0, 10, 1000 or 8000 ppm (equivalent to 0, 16, 159 or 1341 mg/kg/day, respectively) for 18 months, and in male and female Sprague-Dawley rats at 0, 100, 500, or 1000 ppm (equivalent to 0, 5.4, 27 or 557 mg/kg/day, respectively) for two years. There was no evidence of carcinogenicity in either species. Sulfosate is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans" based on the absence of carcinogenicity in mice and rats in two acceptable studies. Based on the available mutagenicity studies, there is no concern for mutagenicity (TXR Nos. 0006452 and 0011156).

D. Subchronic and Chronic Toxicity Studies

1. Subchronic Toxicity

In a 90-day feeding study (MRID No. 00036803) CD-1 mice were fed diets containing 0, 250, 500 or 2500 mg/kg/day of glyphosate for three months. Body weight gains of the high-dose males and females were about 24% and 18% lower, respectively, than those of the controls. Body weight gains of the low-dose and mid-dose groups were comparable to those of the controls. For systemic toxicity, the NOAEL is 500 mg/kg/day and the LOAEL is 2500 mg/kg/day, based on decreased body weight gain in both sexes.

In a 90-day feeding study (MRID No. 40559401), Sprague-Dawley rats were fed diets containing 0, 63, 317, and 1267 mg/kg/day of glyphosate, respectively in males and 0, 84, 404 and 1623 mg/kg/day of glyphosate, respectively, in females. Treatment-related findings were: (1) increased serum phosphorus and potassium in all treated groups, males and females; (2) increased serum glucose in the mid-dose and high-dose males; (3) increased blood urea nitrogen (BUN) and serum alkaline phosphatase in the high-dose males; and (4) occurrence of pancreatic lesions in the high-dose males (pancreas was not examined at the low-dose and mid-dose groups). Based on these findings, the systemic NOAEL is <1000 ppm (not determined definitively) for both sexes.

2. Chronic Toxicity

(i) Rats

A chronic feeding/carcinogenicity study (MRID No. 00093879) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 30, 100, or 300 ppm of glyphosate for 26 months. These levels were equivalent to 0, 3, 10, and 34 mg of glyphosate/kg/day, respectively. There were no effects based on any of the parameters examined (toxic signs, mortality, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights and organ/tissue pathology). Therefore, the NOAEL for systemic toxicity is 300 ppm (males: 31 mg/kg/day and females: 34 mg/kg/day).

A second chronic feeding/carcinogenicity study (MRID No. 41643801) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 2000, 8000, or 20,000 ppm of glyphosate for two years. These levels were equivalent to 0, 89, 362, or 940 mg/kg/day, respectively, for the males and 0, 113, 457, or 1183 mg/kg/day, respectively, for the females. Treatment-related effects observed only in the high-dose group included: (1) decreased body weight gain in females; and (2) increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight, and increased liver weight/brain weight ratio (relative liver weight) in males. No significant systemic effects were observed in the low-dose and mid-dose male and female groups. Therefore, the NOAEL for systemic toxicity is 8000 ppm (males: 362 mg/kg/day and females: 457 mg/kg/day) and the LOAEL is 20,000.

In a combined chronic toxicity/carcinogenicity study (MRID No. 49631701), glyphosate (98.9% a.i.) was administered to 85 Sprague-Dawley rats/sex/dose in the diet for 104 weeks ater 0, 10, 100, 300, and 1000 mg/kg/day to both sexes over the course on the study. Designated for the toxicity portion of the study were 35 rats/sex/dose with the remainder designated for the oncogenicity portion of the study. There were no statistical differences between treated and control groups in survival rates. Pale feces were observed during weeks 16–104 in both sexes at the high dose and in females from the low-mid and high-mid dose levels. No treatment-related effect was observed in food consumption, hematology, ophthalmology, and gross pathology data. Males from the high-dose group had statistically lower mean body weight ($P \leq 0.01$) by 5% to 11% beginning Week 2 of the study until Week 104, and at termination was 10% lower (-14% weight gain). Females at the high dose had statistically lower body weight ($P \leq 0.05$) by 5% to 12% beginning Week 20 through Week 80 (with several exceptions), and at termination was 8% lower (-11% weight gain). Statistically increased ALP activities (+46% to +72%) were observed in males at the high dose throughout the study except for the 51 week interval when the mean value was 31% higher than control. Elevated ALP activities were observed in females at the high dose (+34% to +53%) throughout the study, and through most of the study at the high-mid dose by +20% to +67%, though not always statistically significant. Urinalysis data showed reduced pH (5.5–6) in males at the high dose throughout the study.

The absolute liver weight was decreased significantly in females at the high dose after 52 weeks, but after correcting for final body weight the difference was statistically significant at the three highest doses. The parotid salivary gland weight was increased significantly in males at the three highest doses (56–111%) after 52 weeks, but not after 104 weeks. The combined weight of the sublingual and submaxillary salivary glands was significantly increased by 13% (22% after correcting for body weight) at the high dose after 52 weeks. In females, the parotid gland was not affected but the sublingual and submaxillary combined weight was significantly higher by about 15%. The changes in salivary gland weights were accompanied by increased incidence of mild to severe parotid salivary gland cell alterations and slight to moderate mandibular salivary gland cell alterations were observed in both sexes at the 52-week and 104-week intervals. The lesions were described as cells and/or acini that appeared larger and stained in a weakly basophilic manner without showing a tendency toward proliferative or degenerative changes over time. In males, the increased incidence and severity of lesions in the parotid gland were significant ($P \leq 0.01$) at 100, 300, and 1000 mg/kg bw/day at 52 weeks, and significant at 300 and 1000 mg/kg bw/day at 104 weeks. The increased incidence of lesions in the mandibular gland were significant at 300 and 1000 mg/kg bw/day at 52 weeks and significant ($P \leq 0.001$) at 100, 300, and 1000 mg/kg bw/day at 104 weeks. In females, the increased incidence of parotid lesions was significant at 300 and 1000 mg/kg bw/day at 52 weeks, and significant at 100, 300, and 1000 mg/kg bw/day at 104 weeks. The increased incidence in the mandibular gland lesions was significant at the high dose at both 52 and 104 weeks. The incidence and/or severity of kidney nephropathy decreased in males at 100, 300, and 1000 mg/kg bw/day at 52 weeks and at the high dose at 104 weeks. Urothelial hyperplasia significantly decreased in females from the high dose group at both the 52-week and 104-week intervals. The LOAEL in male and female Sprague-Dawley rats administered glyphosate for 104 weeks in the diet was 100 mg/kg bw/day based on microscopic lesions in the parotid and mandibular salivary glands. The NOAEL was 10 mg/kg bw/day (MRID No. 49631701).

In another chronic toxicity/carcinogenicity study (MRID No. 49704601), groups of 52 male and 52 female Alpk:APSD (Wistar-derived) rats were fed diets containing glyphosate at 0, 2000, 6000, or 20,000 ppm for two years. These doses were equivalent to 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437, or 1498 mg/kg/day in females, respectively. Treatment-related findings were confined to the liver and kidneys at the highest dose (20,000 ppm). In both sexes, treatment-related changes manifested as papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, and hematuria. The LOAEL was 20,000 ppm (1214 mg/kg/day in males and 1498 mg/kg/day in females) and the NOAEL was 6000 ppm (361 mg/kg/day in males and 437 mg/kg/day in females)

(ii) Mice

In a carcinogenicity study (MRID No. 00251007), glyphosate (Technical, 99.7% a.i.) was administered to groups of 50 male and 50 female CD-1 mice/sex/dose in the diet at dose levels of 0, 1000, 5000, or 30,000 ppm (approximately equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Cage-side and detailed clinical observations were done. Body weight and food intake were monitored throughout the study. Water consumption was measured during months 12 and 24. Erythrocyte, as well as total

white cell counts and differentials, were done at months 12, 18, and 24. Tissues and organs were collected from all mice whether dying during the study or at terminal sacrifice. Microscopic analyses were done on all collected tissues.

No treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The terminal body weight of high-dose males was significantly decreased 9% while the absolute liver weight of high-dose males was significantly decreased 16%; however, no significant treatment-related effects were found on the liver-to-body-weight ratio. The absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17. Neither were statistically significant, and no microscopic histological correlates were found. The incidences of centrilobular hepatocyte hypertrophy were slightly, but not significantly increased in high-dose male mice. Centrilobular hepatocyte necrosis was significantly higher in high-dose males (10/50** (20%) vs. control 2/49 (4%), $P \leq 0.01$). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice; however, proximal tubular epithelial basophilia was significantly increased in high-dose females (9/50 (18%) vs control 0/50 (0%), $P \leq 0.01$). No other microscopic treatment-related effects were found. Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for males and 6069 mg/kg bw/day for females). The NOAEL for the study was 835 mg/kg bw/day for males and 968 mg/kg bw/day for females) (MRID No. 00251007).

In another carcinogenicity study (MRID No. 49631702), glyphosate (97.5–100.2% a.i.) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. Mortality, body weight, body weight gain, and food consumption were monitored throughout the study. WBC differential counts were done during Weeks 52, 77, and 102 of the study. Organ weights were measured and tissues collected for microscopic analyses. Treatment of male and female mice for 104 weeks did not increase mortality and did not decrease body weight, body weight gain or food consumption. No treatment-related clinical signs of toxicity were observed and no effects were found on WBC differential counts. Treatment did increase the absolute and relative thymus weights of male and female mice treated with 300 or 1000 mg/kg bw/day approximately 2–3-fold, but only the results of male mice were statistically increased. However, no treatment-related effects were found microscopically. At necropsy, the incidence of lung masses was slightly increased in high-dose male mice, but were considered coincidental. Microscopically, there was a slight, but statistically significant increase in mineral deposition in the brains of mid- and high-dose male mice. A non-significant increase was observed in female mice. Kidney cysts were also slightly but statistically increased in low- and mid-dose males, but no increase of cortical tubular eosinophilic droplets was found in female mice. The significance of these findings is questionable since they did not follow a dose-response. The systemic NOAEL for glyphosate in male and female CD-1 mice treated up to 104 weeks was 1000 mg/kg bw/day. A LOAEL was not identified (MRID No. 49631702).

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

A. Evidence for Carcinogenicity in Humans

The CARC evaluated one cohort study and seven nested case-control studies based on the cohort study population and twenty-five case-control studies that examined the association between glyphosate exposure and one or more cancer outcomes.

1. Cancer at Multiple Sites

Several case-control studies reported no association for cancer of the oral cavity, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, breast or melanoma from exposure to glyphosate (De Roos *et al.*, 2005; Engle *et al.*, 2005; Lee *et al.*, 2007; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010).

In single case-control studies, no associations were found for cancers of the esophagus, stomach, prostate or soft-tissue sarcoma from exposure to glyphosate (Alavanja *et al.*, 2003; Lee *et al.*, 2004; Band *et al.*, 2011; Pahwa, *et al.*, 2011; Koutros *et al.,* 2013). No association for childhood cancer was found from maternal or paternal exposure to glyphosate (Flower *et al.*, 2004).

2. Brain Cancer

A case-control study in Nebraska and the Upper Midwest Health case-control study in Iowa, Michigan, Minnesota and Wisconsin did not find any no association of glyphosate with adult brain cancer, specifically for gliomas (Ruder *et al.*, 2004; Carreon *et al.*, 2005; and Lee *et al.*, 2005).

3. Leukemia

No significant association with leukemia was reported in a case-control study in Iowa and Minnesota (Brown *et al.*, 1990) or in the AHS cohort (De Roos *et al.*, 2005). A Swedish case-control study reported a non-statistically significant elevated risk for hairy cell leukemia. However, the authors stipulated that this risk should be interpreted with caution since it was based on only 4 glyphosate-exposed cases (Nordstrom *et al.*, 1998).

4. Multiple Myeloma

No significant association for multiple myeloma from exposure to glyphosate was found in three separate population-based case-control studies: one in Iowa and Minnesota (Brown *et al.*, 1993) and the other in Iowa and North Carolina, USA (De Roos *et al.*, 2005; Sorhan 2015); and the third study in Canada (Pahwa *et al.*, 2012; Kachuri *et al.*, 2013), and in a hospital-based case-control study in France (Orsi *et al.*, 2009). A cohort study found no association with glyphosate exposure and monoclonal gammopathy of undetermined significance, a pre-clinical marker of multiple myeloma progression (Landgren *et al.*, 2009).

5. Non-Hodgkin Lymphoma

There is conflicting evidence for an association between glyphosate exposure and NHL; seven case-control studies reported no association in the U.S, Canada, and France, while two case-control studies from Sweden reported positive association.

No association between glyphosate exposure and NHL was found in four population-based case-control studies in the United States: in Iowa and Minnesota (Cantor *et al.*, 1992); in Iowa, Nebraska and Minnesota (Lee *et al.*, 2004a); in Iowa, Nebraska, Minnesota and Kansas (De Roos *et al.*, 2003) and in the AHS cohort with 57,311 licensed pesticide applicators in Iowa and North Carolina (De Roos *et al.*, 2005).

Similarly, no association between glyphosate exposure and NHL was seen in two population-based case-control studies conducted in various Canadian provinces (McDuffie *et al.*, 2001; Hohenadel *et al.,* 2011).

A hospital based case-control study from France did not find an association between glyphosate exposure and NHL (Orsi *et al.*, 2009).

The first report of an association between glyphosate exposure and NHL was in a population-based case-control study from Sweden (OR=23.3; 95% CI=0.40–13.0); however, this finding was based on only 4 glyphosate-exposed cases and 3 controls (Hardell and Erickson, 1999).

In a 2002 follow-up study, data from two case-control studies in Sweden, one on NHL and the other on hairy cell leukemia, were pooled and analyzed. A univariate analysis showed an increased risk (OR=3.04; 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, risk declined (OR=1.85; 95% CI=0.55–6.20) (Hardell *et al.*, 2002).

In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analyses showed a statistically significantly increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51) (Erickson *et al.*, 2008).

A meta-analysis of the six studies (De Roos *et al.,* 2003; 2005; McDuffie *et al.*, 2001; Hardell *et al.*, 2002; Erickson *et al.*, 2008; and Orsi *et al.*, 2009) that showed an association between glyphosate exposure and NHL, resulted in a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014).

In an attempt to address the noted power/sample size issues and after considering the adjusted estimates of the two Swedish studies, IARC performed a meta-analysis of the data and estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65) (IARC, 2015).

In summary, the epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and non-solid tumors: leukemia, multiple myeloma or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate exposure and NHL. Multiple case-control studies and one prospective cohort study found no association with NHL; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data. The CARC recognizes the meta-analysis conducted by IARC to try to address the power/sample size issues. However, given the limitations of the studies used, a different weighting scheme could easily change the meta-risk ratio. Thus, while the epidemiologic literature to date does not support causal association, the CARC recommends that the literature continue to be monitored for studies related to glyphosate and risk of NHL.

B. Evidence for Carcinogenicity in Experimental Animals

1. Evidence for Carcinogenicity in Rats

A total of seven chronic toxicity/carcinogenicity studies in Wistar or Sprague-Dawley strain rats were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 3.0 mg/kg/day to 1500 mg/kg/day for 2-years.

(i) Testes

In Sprague-Dawley rats (MRID No. 00093879), there was a non-dose-related increase in the incidences of interstitial cell tumors in the testes of males at 3 mg/kg/day (6%), 10 mg/kg/day (2%) and 30 mg/kg/day (12%; P=0.013) when compared to controls (0%). The CARC reaffirmed the previous conclusion that these tumors are not treatment related based on the following considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5; range, 3.4% to 6.7%;) and 5) this finding is not replicated in the other studies in the same strain of rats (*i.e.*, no interstitial cell tumors were seen when tested up to 1100 mg/kg/day). The CARC concluded that the interstitial cell tumors are not treatment-related.

(ii) Pancreas

Benign pancreatic islet cell tumors were seen in male Sprague-Dawley rats in two studies. In the first study (MRID No. 00093879), there was no dose response or statistical significance; the incidences for adenomas were: 0%, 10%, 4% and 4% at the control, low, mid, and high dose groups. Carcinomas were seen in one rat at the high dose. In the second study (MRID No. 41643801), there was a statistically significant increase in adenomas at the lowest (100 mg/kg/day) and the highest (1000 mg/kg/day) doses compared to controls: lowest dose, 8/45 (18%; P=0.018); intermediate dose, 5/49 (10%); and highest dose, 7/48 (15%; P=0.042) versus controls, 1/43 (2%). The CARC reaffirmed the previous conclusion that the benign pancreatic islet cell tumors are not treatment-related due to lack of dose-response, absence of pre-neoplastic lesions, lack of progression to malignancy, and incidences within the historical control range (0–17%) reported for this tumor in this strain of rats. This neoplasm was not seen in the other five studies. The CARC concluded that the pancreatic islet tumors are not treatment-related.

(iii) Liver

In male Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of hepatocellular adenomas (P=0.016). The CARC concluded that the minimal increase in adenomas is not treatment-related due lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions, no progression to malignancy, and the incidences were within the historical control range (1.4–18.3%) of the testing laboratory.

In male Wistar rats (MRID No. 49704601), there was a statistically significant trend (P=0.00804) and pairwise significance for the increase in hepatocellular adenomas at the highest (1214 mg/kg/day) dose compared to controls: lowest dose, 2/52 (4%); intermediate dose, 0/52 (0%); and highest dose, 5/52 (10%; P=0.02826) versus controls, 0/52 (0%). The CARC concluded that this increase is not attributable to treatment based on the following considerations: 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the historical control range (0–11.5%).

The CARC noted that survival was better at the high dose (25/52; 13%) compared to the controls (16/52; 8.3%) which could be reason for the slightly higher incidence (5/52) of age-related background tumors like liver adenomas in the absence of any associated lesions. Furthermore, with a weak genotoxic effect one would expect to see an effect on carcinomas (or at least adenomas/ carcinomas, combined) and shorter latency period, which were not observed in this study. With a weak cytotoxic or mitogenic effect one would expect to see an increase in foci and other non-neoplastic lesions. In addition, as discussed above, only a linear trend (no pairwise) was seen for this tumor type in another strain (Sprague-Dawley) for rats where the incidences were still within the historical control range. Also, liver tumors were not seen in the other four studies. This provides additional evidence for lack of an actual carcinogenic response in the liver. The CARC concluded that the liver tumors are not treatment-related.

(iv) Thyroid

In Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of thyroid C-cell tumors in females (P=0.031). The CARC concluded that the minimal increase is not treatment-related due to lack of statistical significance in pairwise comparison, no progression to carcinomas, no increase in severity of grade or incidence of hyperplasia, and the incidences were within the historical control range (3.3–10%). The CARC concluded that the thyroid tumors in female rats are not treatment-related.

In summary, dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female Sprague-Dawley or Wistar rats.

2. Evidence for Carcinogenicity in Mice

Four carcinogenicity studies in CD-1 mice were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 85 mg/kg/day to 4800 mg/kg/day for 18–24 months. In one study there were no statistically significant or otherwise notable increases in the occurrence of any tumor types. Tumors observed in the other three studies are discussed below.

(i) Kidney

Kidney (renal tubular) tumors were seen in male CD-1 mice in one study (MRID No. 00251007). The incidences of adenomas was 1/49 (2%), 0/49 (0%), 0/50 (0%), and 1/50 (2%) in the control (0 mg/k/day), low- (157 mg/kg/day), mid- (814 mg/kg/day) and high-dose (4945 mg/kg/day) groups, respectively. The incidence of carcinomas was 0/49 (0%), 0/49 (0%), 1/50 (2%) and 2/50 (4%) in the control, low-, mid- and high-dose groups, respectively. The incidence of adenomas or carcinoma (combined) was 1/49 (2%), 0/50 (0%), 1/50 (2%), and 3/50 (6%) in the control, low-, mid-, and high-dose groups, respectively. None of these differences showed statistical significance.

The CARC reaffirmed the previous conclusion that the kidney tumors are not treatment-related based on the following weight-of-evidence considerations: a) lack of dose-related trend or statistical significance in pairwise comparisons; b) lack of non-neoplastic renal tubular lesions (*e.g.* tubular necrosis/regeneration, hyperplasia, or basophilia); c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well; and d) the difference in incidence between high-dose group (3/50) and the control group (1/49) was minimal, especially considering the very high concentration given (4 x time the limit dose).

Furthermore, the Pathology Work Group concluded that the renal tumors were not treatment-related since none of the treatment groups differed from the controls for a linear trend or pairwise statistical significance, there was no treatment-related nephrotoxic lesions including pre-neoplastic changes, and multiple renal tumors were not seen in any animal.

In addition, the CARC noted that renal tumors were not observed when tested at a similar dose (4348 mg/kg/day) in this strain of mice in another study(Arysta, 1997b) or in two other studies at the limit dose (MRID No. 49631702, Nufarm, 2009b). If really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000 – 4000 mg/kg/day.

(ii) Lung adenocarcinoma

There was a dose-dependent increase in the incidence of bronchiolar-alveolar adenocarcinoma of the lung in male CD-1 mice (Nufarm, 2009b). There was a positive trend (P=0.02906) in the incidence of lung adenocarcinomas: 5/51 (10%), 5/51 (10%), 7/51 (14%) and 11/51 (22%) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related due to lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions in the lung (*e.g.*, bronchiolar-alveolar hyperplasia), and incidences in all treated groups within the background range (1.42–26%) for this tumor in this strain and age of mice. Also, lung tumors were not seen when tested at a comparable dose (1000 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other three studies (MRID Nos. 00251007; 49631702; Arysta, 1997b).

(iii) Lymphoma/Lymphosarcomas

There was a dose-dependent and statistically significant increase in the incidence of malignant lymphomas in male mice (Nufarm, 2009b). The incidence was: 0/51 (0%; trend P=0.006633), 1/51 (2%), 2/51 (4%) and 5/51 (10%; P=0.02820) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related since the incidences in the concurrent controls (0%) were not representative of the normal background incidences noted in the historical controls (mean, 4.5%; range, 1.5% to 21.7%), and the apparent statistical significance of the pairwise comparison of the high dose group with the concurrent control might have been attributable to this factor rather than an actual carcinogenic response. Also, this neoplasm was not seen in other studies in this strain of mice. For example, in the study by Knezevich and Hogan 1983 (MRID No. 00251007), there was no significant difference in the incidence of lymphomas between control and high-dose groups (P=1.00 for males, P=0.12 for females). In the study by Atkinson *et al.* (1993) (MRID No. 496317), the incidence values in "lymphoreticular/ hematopoietic tissue" were not significantly different between control and high-dose groups (males: 4 in controls, 6 in high-dose group; females: 14 in controls, 13 in high-dose group). In the Arysta 1997 study (Greim *et al.*, 2015), the incidence of lymphoma in males was 2/50, 2/50, 0/51, 6/50 in the control, low, mid and high dose groups, respectively. There were no statistically significant pairwise differences observed in any of these studies.

(iv) Hemangioscarcomas

Hemangiosarcomas were seen in multiple organs including, liver, spleen, and prostate in males and liver and uterus in female CD-1 mice (MRID No. 49631702). There was a positive trend (P=0.00296) in the incidence of hemangiosarcomas in male mice: 0/47 (0%), 0/46 (0%), 0/50 (0%) and 4/45 (9%) at the 0, 100, 300 and 1000 mg/kg/day groups, respectively. The hemangiosarcomas were present in the liver, spleen or prostate in the high dose males. In females, this neoplasm was seen in one female at the low dose (uterus) and in one high dose (spleen). The CARC did not consider the hemangiosarcomas in males to be treatment-related based on the following considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed in mice as spontaneous tumors and are generally more common in males in CD-1 strain mice; 5) there was not a significant increase in hemangiosarcomas seen in the other three mouse studies; and 6) if really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000-4000 mg/kg/day.

In summary, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female CD-1 mice.

C. Discussion

When determining the carcinogenic potential of chemicals, the IARC identifies a cancer "hazard" if an agent (*e.g.*, chemical) is capable of causing cancer under some circumstance and the agent is termed "carcinogenic" if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The IARC also considers that there is "*sufficient evidence of carcinogenicity"* based on the occurrence of increased tumors (benign, malignant, or combination) in: 1) two or more species of animals; 2) two or more independent studies in one species; and/or 3) an increased incidence of tumors in both sexes of a single species. Furthermore, a single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites (IARC Preamble, 2006).

In March 2015, the IARC evaluated the carcinogenic potential of glyphosate. The IARC determined that there was a positive trend in the incidence of a rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. Thus, in accordance with one of the preamble criteria, "the occurrence of tumors in two studies in one species," IARC determined that there is "sufficient evidence" in experimental animals for the carcinogenicity of glyphosate (IARC, 2015).

In contrast, the USEPA's carcinogenicity classification is based on weight-of-evidence considerations in accordance with the agency's 2005 Guidelines for Carcinogen Risk Assessment. The cancer guideline emphasizes the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. This evaluation is accomplished in a single integrative step after assessing all of the individual lines of evidence. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiological studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insight into the possible mode(s) of action and likelihood of human cancer hazard and risk (USEPA, 2005).

Conclusions for evidence of carcinogenicity are based on the combined strength and coherence of inferences appropriately drawn from all of the available information. The following observations add significance to the tumor findings: tumors in multiple species, strains, or both sexes; dose-related increases; progression of lesions from pre-neoplastic to benign to malignant; proportion of malignant tumors; reduced latency of neoplastic lesions; and both biological and statistical significance of the findings (USEPA, 2005).

The IARC attributed the kidney tumors observed in male CD-1 mice at the high dose in the feeding study (MRID No. 00251007) to treatment since they are rare and there was borderline significance in trend test (P=0.034 for carcinoma and P=0.037 for combined adenoma or carcinoma) in a Cochran-Armitage trend test. However, as shown in Table 14, the agency's statistical analyses did not show a significant trend for either carcinoma (P=0.06345) or the combined adenoma or carcinoma (P=0.06483). In a Fisher's exact test, when compared to the concurrent control, there was no pairwise significance for any tumor type (adenoma, carcinoma, or combined). There were no pre-neoplastic renal tubular lesions such as tubular necrosis/ regeneration, hyperplasia or hypertrophy, despite a high dose level (4945 mg/kg/day) that was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guidelines. Examination of multiple sections of kidneys from all animals by more than one pathologist did not result in any additional neoplasms. Although the highest dose tested (4945 mg/kg/day) was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guideline, the incidence of the kidney tumors was minimal (1/50 adenomas and 2/50 carcinomas) compared to controls (1/49 adenomas). An evaluation by the PWG concluded that the renal tumors are not treatment-related since there were no compound related nephrotoxic lesions, including pre-neoplastic changes, multiple tumors were not found in any animals, and there was no evidence of a significant linear trend at the 0.5 level in a one-tailed Cochran-Armitage test or pairwise significance in a Fisher's exact test. Furthermore, kidney tumors were not seen when tested at lower (85 to 1000 mg/kg/day) doses or at a comparable (4116 mg/kg/day) dose in this strain of mice in the other three studies. Thus, the totality of data available from 4 carcinogenicity studies provides a strong support for the conclusion that the kidney tumors seen in one study is not the result of a carcinogenic response to glyphosate.

The IARC attributed the hemangiosarcomas observed in male CD-1 mice at the high dose in separate feeding study (MRID No. 49631702) to treatment due to the positive trend (P<0.001) in a Cochran-Armitage trend test. As shown in Table 16, the agency's statistical analyses also showed a positive trend (P=0.00296) in the trend test. In the Fisher's exact test, there was no pairwise significance when compared to controls. In contrast with the IARC, the CARC did not consider the hemangiosarcomas to be treatment-related based on the following weight-of-evidence considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed as spontaneous tumors in male CD-1 strain mice; and 5) hemangiosarcomas were not seen when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other studies (MRID No.00251007, Arysta, 1997b, Nufarm, 2009b). It is noted that JMPR in their evaluation also concluded that the hemangiosarcomas are not treatment-related owing to lack of dose-response relationship, lack of statistical significance and incidences within the historical control range (JMPR, 2004).

Hemangiosarcomas have similar histopathological features in rodents and humans but differ in both incidence and tissue site. In human populations, hemangiosarcomas have an incidence rate of approximately 0.2 new cases/100,000 people (0.0002%) (1996–2000, US National Cancer Institute–SEER Database) and account for <1% of all human sarcomas. The historical background incidence of hemangiosarcomas in B6C3F1 and CD-1 mice relative to the incidence rate in humans has thus been estimated to be approximately 10,000-fold higher than in people (Pegg *et al.,* 2012). The most common sites for spontaneous hemangiosarcomas in rodents are liver, spleen, bone marrow, and to a lesser extent in lymph nodes and skin (see references in Pegg *et al.* (2012). In male mice, liver and spleen tend to be the most common sites. Human hemangiosarcoma is most commonly reported in skin (Weiss *et al.*, 2001). Primary liver hemangiosarcoma in humans has been linked to chemical exposure, notably thorotrast and vinyl chloride, which are both considered genotoxic carcinogens. There are several examples of induction of hemangiosarcomas by non-genotoxic agents in mice, but no clear examples of hemangiosarcoma induction by non-genotoxic agents in human populations (Cohen *et al.,* 2009). Several studies have looked at potential mode of action (MOA) for these tumors in mice in response to various drugs or chemicals. These MOAs generally relate to hypoxia or vascular toxicity as early key events.

1. Mutagenicity

Glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronucleus assay studies. There is no convincing evidence that the DNA damage is a direct effect of glyphosate, but under some conditions may be secondary to cytotoxicity or oxidative damage. Furthermore, the chemical structure of glyphosate, with its absence of alkyl groups also provides SAR support for the lack of mutagenic/genotoxic potential.

IARC concluded that "there is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic"; however, the IARC analysis included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e.*, no purity information was provided). The CARC did not include such studies in their evaluation. The IARC analysis also focused on DNA damage as an endpoint (*e.g.*, comet assay); however, DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited, where positive findings were reported for chromosomal damage, had study limitations confounding the interpretation of the results. In addition, these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. This includes many negative studies cited by Kier and Kirkland (2013) that were considered by CARC, but were not included in the IARC decision.

2. Structure Activity Relationship

Sulfosate (the trimethylsulfonium salt of glyphosate) is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans," based on the lack of evidence of carcinogenicity in mice and rats in two acceptable studies, and absence of mutagenicity concern.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, glyphosate is classified as "Not Likely to be Carcinogenic to Humans." This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at

doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Not required.

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Cc: Jones, Jim[Jones.Jim@epa.gov]
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Subject: Options on BNA story?

Ex. 5 - Deliberative Process

http://www.bna.com/epa-panel-finds-n57982070575/

EPA Panel Finds Glyphosate Not Likely to Cause Cancer

From Daily Environment Report™

By David Schultz

May 2 — Glyphosate, a weed killer developed by Monsanto that is now the most widely used pesticide in the U.S., likely does not cause cancer, according to an Environmental Protection Agency review panel.

The EPA's Cancer Assessment Review Committee made the determination after analyzing several dozen published and unpublished scientific studies of the chemical. The committee finalized its report on Oct. 1, 2015, but did not release it to the public until late April, when the agency inadvertently posted the report online.

The report's findings disagree with a 2015 review of glyphosate by the World Health Organization's International Agency for Research on Cancer (IARC), which found that the pesticide is a "probable carcinogen" (59 DEN A-10, 3/27/15).

WHO's Findings Disputed

The EPA cancer review committee, led by staffers from the Health Effects Division of the agency's Office of Pesticide Programs, poked a number of holes in the methodology used by IARC for its review of glyphosate, which is the active ingredient in Monsanto's Roundup herbicide as well as hundreds of other products made by dozens of other companies.

For example, the EPA report noted that the IARC scientists disregarded several studies on the effects of exposure to glyphosate because these studies showed no positive results. The EPA report also said the studies IARC chose to include in its review had significant limitations.

Release of the IARC finding on glyphosate had serious negative consequences for the agricultural chemical industry.

It was the basis for a decision by California to require all products containing glyphosate to be listed as carcinogenic, a decision that Monsanto is challenging in court (173 DEN A-6, 9/8/15).

The IARC finding also led to numerous product liability lawsuits against Monsanto from people arguing that exposure to the company's pesticide was the cause of their illnesses (230 DEN A-9, 12/1/15).

Monsanto Statement

"No pesticide regulator in the world considers glyphosate to be a carcinogen, and this conclusion by the U.S. EPA once again reinforces this important fact," Monsanto CEO Hugh

Grant said in a statement. “Unfortunately, last year’s inconsistent classification by IARC generated unwarranted concern and confusion about this important agricultural tool.”
The IARC did not immediately respond to requests from Bloomberg BNA for comment.
The EPA review committee's findings are part of a broader look by the agency at the overall health and environmental effects of glyphosate as a part of its registration review program, which conducts risk reviews of every pesticide chemical once every 15 years.
If the EPA determines that the science shows that the way glyphosate is being used now exceeds acceptable risks, it can enact use restrictions on the chemical or take it off the market altogether.

Report Posted April 29

The EPA posted the cancer review committee's report April 29, along with more than a dozen other glyphosate-related documents, to Regulations.gov, an online document repository for federal agencies.
Then, after the report had been widely spread on social media, the cancer review committee's report and the other documents were removed from the EPA website on the afternoon of May 2.
“Preliminary glyphosate documents were inadvertently posted to the Agency’s docket,” EPA spokeswoman Melissa Harrison told Bloomberg BNA via e-mail. “These documents have now been taken down because our assessment is not final.”

Label Changes?

Some of the other documents the EPA briefly made public pertained to two meetings pesticide regulators held with Monsanto representatives in the year after the IARC review was published.
A slide presentation made at one of these meetings by Monsanto representatives indicated the company may be willing to make voluntary changes to the labels of its glyphosate products to address concerns that they're harming the habitats of certain pollinating insects, including the monarch butterfly.
This document, along with summaries of the discussions during the company's two meetings with EPA pesticide regulators, were among those removed from Regulations.gov.
To contact the reporter on this story: David Schultz in Washington atdschultz@bna.com
To contact the editor responsible for this story: Larry Pearl atlpearl@bna.com

For More Information

A copy of the EPA's Cancer Assessment Review Committee report on glyphosate is available at http://src.bna.com/eAi.
A brief summary of EPA's meeting March 30, 2015, with Monsanto representatives is available at http://src.bna.com/eBJ.
A brief summary of EPA's meeting June 4, 2015, with Monsanto representatives is available at http://src.bna.com/eBL.
A copy of the slide presentation Monsanto representatives made for EPA pesticide regulators last year is available athttp://src.bna.com/eBx.

Melissa J. Harrison

Press Secretary

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Ex. 5 - Deliberative Process

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Cc: Jones, Jim
Subject: Options on BNA story?

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From: Strauss, Linda
Sent: Tue 5/3/2016 3:33:52 PM
Subject: glyphosate docket news

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EPA takes offline report that says glyphosate not likely carcinogenic

CattleNetwork.com - 13 minutes ago

The 86-page report, seen by Reuters and published on Friday on the regulations.gov website that the **EPA** manages, was from the **EPA's** cancer assessment

review committee (CARC). It found that **glyphosate**, the active ingredient in the world's mostly widely ...

EPA Quickly Takes Study Offline Showing No Evidence Weed Killer Causes Cancer

Daily Caller - 49 minutes ago

The CARC study ripped offline by **EPA**, however, rebutted IARC's conclusions, saying they were based on flawed

studies, some of which weren't even reproduced by other scientists. CARC ultimately ruled **glyphosate** is “not likely to be carcinogenic in **...**

EPA Takes Down Report Saying Glyphosate Not Carcinogenic

KTIC - 1 hour ago

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EPA's glyphosate cancer finding not ready for primetime

Politico - 1 hour ago

EPA'S GLYPHOSATE CANCER FINDING NOT READY FOR PRIMETIME: The **EPA** has made a preliminary finding that **glyphosate** is unlikely to cause

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Glyphosate 'not likely to be carcinogenic to humans'

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This determination is the published conclusion of **EPA's** Cancer Assessment Review Committee (CARC) and is based on the overwhelming weight of evidence on **glyphosate**. EPAs

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EPA pulls report that says glyphosate not likely carcinogenic

AG Week - 1 hour ago

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EPA Panel Finds Glyphosate Not Likely to Cause Cancer

Bloomberg BNA - 3 hours ago

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EPA takes offline a report that says glyphosate not likely carcinogenic

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EPA takes offline report that says glyphosate not likely carcinogenic

Business Insider - 12 hours ago

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STLtoday.com - 11 hours ago

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What Is Going On With Glyphosate? EPA's Odd Handling of Controversial Chemical

U.S. Right

to Know (press release) (blog) - 11 hours ago

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EPA takes offline report that says

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Town Hall - 14 hours ago

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EconomyNext - 14 hours ago

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Huffington Post - 14 hours ago

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Channel News Asia - 14 hours ago

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Reuters UK - 14 hours ago

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WHTC - 14 hours ago

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WHBL Sheboygan - 14 hours ago

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KFGO - 14 hours ago

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KDAL - 14 hours ago

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Yahoo News - 14 hours ago

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Daily Mail - 14 hours ago

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Reuters Africa - 14 hours ago

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Thomson Reuters Foundation - 14 hours ago

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Once Again, EPA Concludes That Glyphosate Does Not Cause Cancer

Digital Journal - 18 hours ago

ST. LOUIS-- (Business Wire)-- As part of its ongoing registration review of the herbicide **glyphosate**, the U.S. Environmental Protection Agency (**EPA**) has published its official classification of **glyphosate** as “Not Likely to be Carcinogenic to Humans.

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Business Wire (press release) - 18 hours ago

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1 2 Next

To: Jones, Jim[Jones.Jim@epa.gov]
From: Chris Portier
Sent: Wed 5/4/2016 11:38:18 AM
Subject: Fwd: glyphosate: POLITICO on EPA report

;;;;Jim,
FYI.

C.

Subject: glyphosate: POLITICO on EPA report

GLYPHOSATE STORM'S A-BREWIN': The U.S. Environmental Protection Agency has made a preliminary finding that glyphosate is unlikely to cause cancer in humans — but the agency isn't ready to go public yet. The EPA briefly posted online an October 2015 final report from its Cancer Assessment Review Committee, which concluded glyphosate is "not likely to be carcinogenic to humans." It then pulled it from its website. The committee said evidence from existing epidemiological studies and tests of lab animals doesn't meet the bar for classifying the herbicide as a carcinogen. An agency spokesperson told POLITICO the report was removed because assessment was ongoing. "Our assessment will be peer reviewed and completed by end of 2016," said the spokesperson.

— Why this matters for the EU: A political scrum over what to do about glyphosate is underway in the EU. Parliament voted to extend the chemical's authorization for seven years, the Commission is pushing for 10, but the real decision comes in a Plant, Animal, Food and Feed Committee meeting on May 18-19. Advocates for banning glyphosate altogether cite a March 2015 study by International Agency for Research on Cancer, which said it caused cancer. Glyphosate's political supporters cite a November study with the opposite conclusions. This latter group might now have another study in their arsenal — and from a reputable U.S. government agency. "In line with the 90,000 pages, and 3,300 studies already published in support of the reapproval of glyphosate, the EPA report casts yet more doubt on the conclusions of IARC," a spokesperson for the European Crop Protection Association told Morning Agri. Greenpeace EU, which opposes using glyphosate as long as there is no scientific consensus, told Morning Agri it had not yet read the study and so couldn't comment. More: http://reut.rs/23mbxYf.

To: Jones, Jim[Jones.Jim@epa.gov]; Burke, Thomas[Burke.Thomas@epa.gov]
Cc: Mitchell, Stacey[Mitchell.Stacey@epa.gov]
From: Distefano, Nichole
Sent: Wed 5/4/2016 6:12:59 PM
Subject: FW: Letter to Administrator McCarthy
05.04.06 SST Letter to Administrator McCarthy re CARC.pdf

;;;
Oversight letter on glyphosate. We'll be putting together a meeting to discuss. Let me know who from your offices should attend.

Nichole Distefano

Associate Administrator

Office of Congressional and Intergovernmental Relations

Environmental Protection Agency

(202) 564-5200

Distefano.Nichole@epa.gov

LAMAR S. SMITH, Texas
CHAIRMAN

EDDIE BERNICE JOHNSON, Texas
RANKING MEMBER

Congress of the United States
House of Representatives

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

2321 RAYBURN HOUSE OFFICE BUILDING

WASHINGTON, DC 20515–6301

(202) 225–6371
www.science.house.gov

May 4, 2016

The Honorable Gina McCarthy
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Dear Administrator McCarthy:

The Committee on Science, Space, and Technology is conducting oversight of U.S. Environmental Protection Agency's (EPA) risk analysis prepared by the Cancer Assessment Review Committee (CARC). According to recent media reports, on April 29, 2016, EPA posted what appears to be the final risk assessment for glyphosate prepared by CARC (the CARC report).[1] The CARC report indicates that glyphosate is "Not Likely to be Carcinogenic to Humans."[2] Press reports indicate that EPA removed this document on May 2, 2016.[3] Subsequently, EPA has asserted that the analysis of glyphosate is not final and that the documents were posted "inadvertently."[4]

The Committee has reviewed the CARC report and point out that it is clearly marked as a "Final Report."[5] The report also contains the signatures of thirteen members of CARC.[6] However, EPA's removal of this report and the subsequent backtracking on its finality raises questions about the agency's motivation in providing a fair assessment of glyphosate – an assessment based on the scientific analysis conducted by CARC. Furthermore, EPA's apparent mishandling of this report may shed light on larger systemic problems occurring at the agency. In order to assist the Committee in its oversight of the EPA's assessment of glyphosate, please

---

[1] P.J. Huffstutter, *EPA Takes Offline Report that Says Glyphosate Not Likely Carcinogenic,* Reuters, May 2, 2016, *available at* http://www.reuters.com/article/us-usa-glyphosate-epa-idUSKCN0XU01K.
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provide all documents and communications from January 1, 2015, to the present, referring or relating to the CARC report on glyphosate by 5:00 p.m. on May 18, 2016.

The Committee on Science, Space, and Technology has jurisdiction over environmental and scientific programs and "shall review and study on a continuing basis laws, programs, and Government activities" as set forth in House Rule X.

The Committee requests that you provide the requested documents and information, in electronic format. An attachment to this letter provides details on producing documents to the Committee.

If you have any questions about this request, please contact Joseph Brazauskas or Taylor Jordan of the Science, Space, and Technology Committee staff at 202-225-6371. Thank you for your attention to this matter.

Sincerely,

Lamar Smith

Lamar Smith
Chairman

cc: The Honorable Eddie Bernice Johnson, Ranking Minority Member, House Committee on Science, Space and Technology

To: Jones, Jim[Jones.Jim@epa.gov]; Wise, Louise[Wise.Louise@epa.gov]; Mojica, Andrea[Mojica.andrea@epa.gov]
From: Strauss, Linda
Sent: Wed 5/4/2016 8:09:45 PM
Subject: FW: Letter to Administrator McCarthy
05.04.06 SST Letter to Administrator McCarthy re CARC.pdf

....
;;;;
From: Perlis, Robert
Sent: Wednesday, May 04, 2016 3:59 PM
To: Strauss, Linda ; Mojica, Andrea
Subject: FW: Letter to Administrator McCarthy

FYI – this came in today on the glyphosate CARC paper.

Bob Perlis

Pesticides and Toxic Substances Law Office

Office of General Counsel

US EPA

(202) 564-5636

From: Mitchell, Stacey
Sent: Wednesday, May 04, 2016 2:12 PM
To: Mclean, Kevin <Mclean.Kevin@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>
Cc: Rackoff, Jonathan <Rackoff.Jonathan@epa.gov>
Subject: FW: Letter to Administrator McCarthy

FYI

Stacey H. Mitchell

Deputy General Counsel

U.S. Environmental Protection Agency

(202) 564-7614

From: Dickerson, Tom
Sent: Wednesday, May 04, 2016 1:55 PM
To: Distefano, Nichole <DiStefano.Nichole@epa.gov>; Brown, Tristan <Brown.Tristan@epa.gov>; Aarons, Kyle <Aarons.Kyle@epa.gov>; Asher, Jonathan <Asher.Jonathan@epa.gov>; Mitchell, Stacey <Mitchell.Stacey@epa.gov>; Rackoff, Jonathan <Rackoff.Jonathan@epa.gov>; Sublett, Stacey <Sublett.Stacey@epa.gov>

Cc: Moody, Christina <Moody.Christina@epa.gov>; Williams, Thea <Williams.Thea@epa.gov>
Subject: FW: Letter to Administrator McCarthy

A new Smith letter about the Roundup study, asking for document. Assuming Is this primarily an ORD report?

Tom Dickerson

Office of Congressional Relations

U.S. Environmental Protection Agency

(202) 564-3638

From: Brazauskas, Joseph [mailto:Joseph.Brazauskas@mail.house.gov]
Sent: Wednesday, May 04, 2016 1:33 PM
To: Dickerson, Tom <Dickerson.Tom@epa.gov>; Aarons, Kyle <Aarons.Kyle@epa.gov>
Cc: Marin, Mark <Mark.Marin@mail.house.gov>; Jordan, Taylor <Taylor.Jordan@mail.house.gov>; Callen, Ashley <Ashley.Callen@mail.house.gov>
Subject: Letter to Administrator McCarthy

Tom,

Please find attached a letter from Chairman Smith to Administrator McCarthy. Please confirm receipt.

Thank you,

Joe

Joseph A. Brazauskas

Senior Counsel

Committee on Science, Space and Technology

Lamar Smith, Chairman

P: (202) 225-6371

LAMAR S. SMITH, Texas
CHAIRMAN

EDDIE BERNICE JOHNSON, Texas
RANKING MEMBER

Congress of the United States
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COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

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[2] Evaluation of the Carcinogenic Potential of Glyphosate, Final Report, Cancer Assessment Review Committee, U.S. EPA, Oct. 1, 2015, *available at* http://src.bna.com/eAi.
[3] P.J. Huffstutter, *EPA Takes Offline Report that Says Glyphosate Not Likely Carcinogenic,* Reuters, May 2, 2016, *available at* http://www.reuters.com/article/us-usa-glyphosate-epa-idUSKCN0XU01K.
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Sincerely,

Lamar Smith

Lamar Smith
Chairman

cc: The Honorable Eddie Bernice Johnson, Ranking Minority Member, House Committee on Science, Space and Technology

To: Jones, Jim[Jones.Jim@epa.gov]
From: Distefano, Nichole
Sent: Mon 5/9/2016 1:52:35 PM
Subject: FW:

Ex. 5 - Deliberative Process

Nichole Distefano

Associate Administrator

Office of Congressional and Intergovernmental Relations

Environmental Protection Agency

(202) 564-5200

Distefano.Nichole@epa.gov

From: Spencer, Peter [mailto:Peter.Spencer@mail.house.gov]
Sent: Monday, May 09, 2016 9:36 AM
To: Distefano, Nichole
Subject:

Nichole, can you give me a call about this?

PESTICIDES:

Report touting glyphosate safety published by mistake -- EPA

Published: Tuesday, May 3, 2016

U.S. EPA yesterday posted online and then removed a report suggesting glyphosate is unlikely to pose a cancer risk to humans.

The 86-page report was removed because it was not complete, EPA said. The agency said the assessment "is not final" and was posted inadvertently.

The document from EPA's cancer assessment review committee found glyphosate, the active ingredient in the pesticide Roundup, was "not likely to be carcinogenic to humans."

Though EPA said the report was incomplete, its pages were stamped "FINAL" and dated Oct. 1, 2015.

EPA is reviewing the registration of glyphosate. The chemical has been the subject of intense scrutiny because of its widespread use and findings by the International Agency for Research on Cancer that it is a human carcinogen (***Greenwire***, July 15, 2015).

A reporter from Bloomberg BNA first posted a link to the documents yesterday on Twitter (P.J. Huffstutter,

Reuters, May 2). -- **SP**

Peter L. Spencer
Majority Professional Staff
Oversight and Investigations
Committee on Energy and Commerce
U.S. House of Representatives
(202) 225-5736
peter.spencer@mail.house.gov

To: Housenger, Jack[Housenger.Jack@epa.gov]; Mojica, Andrea[Mojica.andrea@epa.gov]; Jones, Jim[Jones.Jim@epa.gov]; Wise, Louise[Wise.Louise@epa.gov]; Perlis, Robert[Perlis.Robert@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]
Cc: Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Sisco, Debby[Sisco.Debby@epa.gov]
From: Keigwin, Richard
Sent: Tue 5/10/2016 2:48:25 PM
Subject: RE: glyphosate draft response for review

Ex. 5 - Deliberative Process

From: Housenger, Jack
Sent: Tuesday, May 10, 2016 10:45 AM
To: Mojica, Andrea ; Jones, Jim ; Wise, Louise ; Keigwin, Richard ; Perlis, Robert ; Strauss, Linda
Cc: Dinkins, Darlene ; Sisco, Debby
Subject: RE: glyphosate draft response for review

A few comments

From: Mojica, Andrea
Sent: Tuesday, May 10, 2016 10:32 AM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Housenger, Jack <Housenger.Jack@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: glyphosate draft response for review

All,

Attached is a draft response to Chairman Lamar Smith's (Committee on Science, Space, and Technology) glyphosate inquiry. I have attached in the incoming letter to the Administrator as well. Please let me know if you have any comments by May 12th.

Thanks,

Andrea

To: Jones, Jim[Jones.Jim@epa.gov]; Keigwin, Richard[Keigwin.Richard@epa.gov]
Cc: Housenger, Jack[Housenger.Jack@epa.gov]; Wise, Louise[Wise.Louise@epa.gov]; Perlis, Robert[Perlis.Robert@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]; Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Sisco, Debby[Sisco.Debby@epa.gov]
From: Mojica, Andrea
Sent: Tue 5/10/2016 5:02:38 PM
Subject: RE: glyphosate draft response for review
draft response to Chairman Smith_glyphosate_10 May 2016_OPP comments.docx

Ex. 5 - Deliberative Process

From: Jones, Jim
Sent: Tuesday, May 10, 2016 12:15 PM
To: Keigwin, Richard
Cc: Housenger, Jack ; Mojica, Andrea ; Wise, Louise ; Perlis, Robert ; Strauss, Linda ; Dinkins, Darlene ; Sisco, Debby
Subject: Re: glyphosate draft response for review

Thx Rick. Jim

Sent from my iPhone

On May 10, 2016, at 10:48 AM, Keigwin, Richard <Keigwin.Richard@epa.gov> wrote:

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Sent: Tuesday, May 10, 2016 10:45 AM
To: Mojica, Andrea <Mojica.andrea@epa.gov>; Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
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Sent: Tuesday, May 10, 2016 10:32 AM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Housenger, Jack <Housenger.Jack@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
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Cc: Wise, Louise[Wise.Louise@epa.gov]; Perlis, Robert[Perlis.Robert@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]; Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Sisco, Debby[Sisco.Debby@epa.gov]
From: Housenger, Jack
Sent: Tue 5/10/2016 5:31:40 PM
Subject: RE: glyphosate draft response for review

Ex. 5 - Deliberative Process

From: Mojica, Andrea
Sent: Tuesday, May 10, 2016 1:03 PM
To: Jones, Jim ; Keigwin, Richard
Cc: Housenger, Jack ; Wise, Louise ; Perlis, Robert ; Strauss, Linda ; Dinkins, Darlene ; Sisco, Debby
Subject: RE: glyphosate draft response for review

Attached is an updated draft addressing Jack and Rick's comments.

From: Jones, Jim
Sent: Tuesday, May 10, 2016 12:15 PM
To: Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: Housenger, Jack <Housenger.Jack@epa.gov>; Mojica, Andrea <Mojica.andrea@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
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Sent from my iPhone

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Ex. 5 - Deliberative Process

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From: Housenger, Jack
Sent: Tuesday, May 10, 2016 10:45 AM
To: Mojica, Andrea <Mojica.andrea@epa.gov>; Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: RE: glyphosate draft response for review

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Sent: Tuesday, May 10, 2016 10:32 AM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Housenger, Jack <Housenger.Jack@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
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Thanks,

Andrea

To: /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8a8880786f8940df91a4308d6c0629f0-JSaxton[/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8a8880786f8940df91a4308d6c0629f0-JSaxton]; /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c52de171eaa64c0f9801c4105e1b5b26-Lewis, Paul[/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c52de171eaa64c0f9801c4105e1b5b26-Lewis, Paul]; /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fee1c9c073ef4e61b4284aa034ccb73c-Deborah J Hartman[/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fee1c9c073ef4e61b4284aa034ccb73c-Deborah J Hartman]; Anderson, Steve[Anderson.Steve@epa.gov]; Askinazi, Valerie[Askinazi.Valerie@epa.gov]; Blunck, Christopher[Blunck.Chris@epa.gov]; Brown, Sam[Brown.Sam@epa.gov]; Buster, Pamela[Buster.Pamela@epa.gov]; Canavan, Sheila[Canavan.Sheila@epa.gov]; Caraballo, Mario[Caraballo.Mario@epa.gov]; Carroll, Megan[Carroll.Megan@epa.gov]; Christian, Myrta[Christian.Myrta@epa.gov]; Cleland-Hamnett, Wendy[Cleland-Hamnett.Wendy@epa.gov]; Corado, Ana[Corado.Ana@epa.gov]; Cunningham-HQ, Barbara[Cunningham-HQ.Barbara@epa.gov]; Davies, Clive[Davies.Clive@epa.gov]; Devito, Steve[Devito.Steve@epa.gov]; Dix, David[Dix.David@epa.gov]; Doa, Maria[Doa.Maria@epa.gov]; Dunton, Cheryl[Dunton.Cheryl@epa.gov]; Ebzery, Joan[Ebzery.Joan@epa.gov]; Edelstein, Rebecca[Edelstein.Rebecca@epa.gov]; Eglsaer, Kristie[Eglsaer.Kristie@epa.gov]; Farquharson, Chenise[Farquharson.Chenise@epa.gov]; Fehrenbacher, Cathy[Fehrenbacher.Cathy@epa.gov]; Flattery, Priscilla[Flattery.Priscilla@epa.gov]; Fort, Felecia[Fort.Felecia@epa.gov]; Frank, Donald[Frank.Donald@epa.gov]; Giamporcaro, David[Giamporcaro.David@epa.gov]; Gibson, Hugh[Gibson.Hugh@epa.gov]; Gimlin, Peter[Gimlin.Peter@epa.gov]; Gorder, Chris[Gorder.Chris@epa.gov]; Gordon, Brittney[Gordon.Brittney@epa.gov]; Grant, Brian[Grant.Brian@epa.gov]; Gray, Shawna[Gray.Shawna@epa.gov]; Guthrie, Christina[Guthrie.Christina@epa.gov]; Henry, Tala[Henry.Tala@epa.gov]; Jones, Jim[Jones.Jim@epa.gov]; Kapust, Edna[Kapust.Edna@epa.gov]; Kemme, Sara[kemme.sara@epa.gov]; Koch, Erin[Koch.Erin@epa.gov]; Krasnic, Toni[krasnic.toni@epa.gov]; Lavoie, Emma[Lavoie.Emma@epa.gov]; Leczynski, Barbara[leczynski.barbara@epa.gov]; Lee, Mari[Lee.Mari@epa.gov]; Leopard, Matthew[Leopard.Matthew@epa.gov]; Lobar, Bryan[Lobar.Bryan@epa.gov]; Mattheisen, Mike[Mattheisen.Mike@epa.gov]; Mclean, Kevin[Mclean.Kevin@epa.gov]; Menasche, Claudia[Menasche.Claudia@epa.gov]; Moose, Lindsay[Moose.Lindsay@epa.gov]; Morris, Jeff[Morris.Jeff@epa.gov]; Moss, Kenneth[Moss.Kenneth@epa.gov]; Mottley, Tanya[Mottley.Tanya@epa.gov]; Myers, Irina[Myers.Irina@epa.gov]; Myrick, Pamela[Myrick.Pamela@epa.gov]; Nazef, Laura[Nazef.Laura@epa.gov]; Owen, Elise[Owen.Elise@epa.gov]; Paquette, Nicole[Paquette.Nicole@epa.gov]; Parsons, Doug[Parsons.Douglas@epa.gov]; Patel, Neil[Patel.Neil@epa.gov]; Penberthy, Ward[Penberthy.Ward@epa.gov]; Pierce, Alison[Pierce.Alison@epa.gov]; Price, Michelle[Price.Michelle@epa.gov]; Reese, Recie[Reese.Recie@epa.gov]; Reisman, Larry[Reisman.Larry@epa.gov]; Rice, Cody[Rice.Cody@epa.gov]; Ross, Philip[Ross.Philip@epa.gov]; Sadowsky, Don[Sadowsky.Don@epa.gov]; Santacroce, Jeffrey[Santacroce.Jeffrey@epa.gov]; Saxton, Dion[Saxton.Dion@epa.gov]; Scarano, Louis[Scarano.Louis@epa.gov]; Schmit, Ryan[schmit.ryan@epa.gov]; Schweer, Greg[Schweer.Greg@epa.gov]; Selby-Mohamadu, Yvette[Selby-Mohamadu.Yvette@epa.gov]; Seltzer, Mark[Seltzer.Mark@epa.gov]; Shafer, Jonathan[shafer.jonathan@epa.gov]; Liva, Aakruti[Liva.Aakruti@epa.gov]; Sherlock, Scott[Sherlock.Scott@epa.gov]; Simons, Andrew[Simons.Andrew@epa.gov]; Sirmons, Chandler[Sirmons.Chandler@epa.gov]; Slotnick, Sue[Slotnick.Sue@epa.gov]; Stedeford, Todd[Stedeford.Todd@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]; Suski, Jamie[Suski.Jamie@epa.gov]; Syed, Hamaad[Syed.Hamaad@epa.gov]; Symmes, Brian[Symmes.Brian@epa.gov]; Szilagyi, Maria[Szilagyi.Maria@epa.gov]; Thompson, Tony[Thompson.Tony@epa.gov]; Tillman, Thomas[Tillman.Thomas@epa.gov]; Tomassoni, Guy[Tomassoni.Guy@epa.gov]; Tran, Chi[Tran.Chi@epa.gov]; Vendinello, Lynn[Vendinello.Lynn@epa.gov]; Wallace, Ryan[Wallace.Ryan@epa.gov]; Wheeler,

Cindy[Wheeler.Cindy@epa.gov]; Widawsky, David[Widawsky.David@epa.gov]; Williams, Aresia[Williams.Aresia@epa.gov]; Williamson, Tracy[Williamson.Tracy@epa.gov]; Wills, Jennifer[Wills.Jennifer@epa.gov]; Wise, Louise[Wise.Louise@epa.gov]; Wright, Tracy[Wright.Tracy@epa.gov]
From: Faeth, Lisa
Sent: Fri 5/13/2016 3:32:29 PM
Subject: News Articles (For EPA Distribution Only)

;;

BNA DAILY ENVIRONMENT REPORT ARTICLES

Nanoscale Rule Proposal Said to Threaten Innovation

BNA Snapshot

Securing Data on Nanoengineered Chemicals

Key Development: The American Coatings Association says the EPA's proposal to require companies to notify the agency 135 days before they make or process a new form of an existing nanoscale chemical threatens innovation.

Why Now: The coatings association and other industry groups are voicing their concerns because the EPA has said it will issue a final data-collection rule by the end of 2016.

By Pat Rizzuto

May 12 — The Environmental Protection Agency's proposal to require companies to notify the agency 135 days before they make or process a new form of an existing nanoscale chemical threatens innovation, according to the American Coatings Association.

"Opportunities to further enhance the properties of coatings, find radically new functionality, conserve resources and reduce solvent emissions will become severely burdensome or completely missed with the implementation of the reporting program as it is currently written," the American Coatings Association (ACA) said in a position paper issued May 10.

The ACA paper highlights benefits of coatings made with nanoengineered chemicals, studies such as one that found the final products—when sanded or sawed—produced no more nanomaterial-containing dust than would conventional coatings and problems the agency's regulatory proposal would cause coatings manufacturers.

The association, which represents manufacturers of paints, car finishes and other coatings, issued the four-page paper in light of a data collection rule the EPA proposed on April 6, 2015 (80 Fed. Reg. 18,330; 58 DEN A-4, 3/26/15).

The EPA proposed rule (RIN:2070–AJ54):

• would define nanoscale materials;

• would establish a one-time reporting obligation for nanoscale materials during which companies would provide the EPA physical form, size, shape and other data about their nanoscale chemical if the manufacturer or processor already had the information; and

• would establish a 135 day notification requirement triggered by manufacturers or processors use of a new, discreet form of a nanoscale chemical.

270-Day Wait

In combination with other requirements, the 135 day notification mandate would mean companies would have to wait 270 days before they could fully commercialize a new nanomaterial, the coatings association said.

The four-page statement is the most recent industry volley against a proposed rule that many different industry sectors say would impose unnecessary obligations and exceeds the agency's regulatory authority.

The coatings association issued the position paper now because the EPA has said it plans to issue a final data collection rule later this year, Stephen Wieroniey, ACA's director of occupational health and product safety, told Bloomberg BNA in an e-mail May 12.

The NanoManufacturing Association, of which ACA is a member, met with EPA officials in February, according to a March 16 letter that association posted online.

Clarification of Rule

Jim Alwood, a program manager in the EPA's Chemical Control Division who coordinates nanotechnology issues under the Toxic Substances Control Act, said in March that the agency will address in any final rule concerns voiced by companies about the 135 day notification and other possible requirements. He discussed the rule at the 2016 Global Chemical Regulations Conference.

Alwood did not say whether the agency would eliminate the 135-day notification requirement, change it or address industry concerns in some other way.

The agency will clarify several terms used in the proposed rule, Alwood said.

He referred to terms such as “unique and novel characteristics or properties” and “trace amounts,” which were described as vague by many organizations that commented on the proposal.

The final rule will request available data about nanoscale chemicals, Alwood said. “The rule does not require anyone to generate data.”

To contact the reporter on this story: Pat Rizzuto in Washington at prizzuto@bna.com

To contact the editor responsible for this story: Larry Pearl at lpearl@bna.com

For More Information

The EPA's proposed rule and other nanoscale chemicals information is available at http://1.usa.gov/1T90w81.

The American Coatings Association position paper is available at http://src.bna.com/eVY.

EPA Tips to Limit Flame Retardant Exposure

May 12 — The Environmental Protection Agency released a flier May 12 offering parents tips on ways they can reduce children's exposure to flame retardants. Exposure to flame retardants, the EPA said, may be associated with a range of health problems, including reduced IQ, learning disorders, reduced fertility, thyroid disruption and cancer. Children may be exposed through contact with products such as nursing pillows, car seats, crib mattresses, baby carriers, strollers, changing pads, upholstered furniture and carpets. The EPA is assessing the risks of flame retardants, the agency said. EPA's flier is available at http://src.bna.com/eWX.

INSIDEEPA.COM ARTICLES

House Lawmakers Tentatively Back TSCA Reform Deal On State Preemption

Top House lawmakers are offering tentative support for a Senate-crafted deal that aims to advance Toxic Substances Control Act (TSCA) reform legislation by resolving a debate over preempting new state chemical requirements with language that appears to give states an additional year to regulate some substances before EPA could preempt them.

EPA Advisors Weigh Chemical Prioritization Tools Ahead Of TSCA Reform

EPA's Chemical Safety Advisory Committee (CSAC) is eyeing whether it should craft recommendations on how the agency can use high throughput screening and other new toxicity testing methods in prioritization of chemicals for risk assessment, reviews that could be bolstered by pending Toxic Substances Control Act (TSCA) reform.

As Lawmakers Near TSCA Reform Deal, Questions Remain On Key Policies

As lawmakers near a potential final deal on legislation to overhaul the Toxic Substances Control Act (TSCA), chemical industry sources say significant questions remain on how an agreement might affect a host of key policies in the bill including preemption of state chemical programs, the scope of EPA risk assessments, and more.

Northeast States To Meet With EPA Over PFCs, Eyeing Lessons Learned

State regulators from the Northeast plan to privately meet with EPA later this month as part of an academic forum in order to exchange information and lessons learned on perfluorinated

chemicals (PFC), a class of chemicals that is drawing growing regulatory and public attention.

Chemical Industry Urges EPA To Change Review Of Controversial Solvent

The chemical industry group American Chemistry Council (ACC) is urging EPA to delay the peer review of a draft risk assessment of 1-bromopropane (1-BP), arguing the members selected to serve on the panel reviewing the solvent are unqualified and raising concerns about the process the agency used to create a larger committee overseeing the peer review panel.

GREENWIRE ARTICLES

EPA Employees 'anxious' about 'scary' Trump

Karen Kellen, who represents thousands of U.S. EPA workers as president of the American Federation of Government Employees Council 238, has one word about what Donald Trump as president could mean for the agency.

"Scary," said Kellen.

Trump, the real estate tycoon and reality television star, is now the Republican Party's presumptive 2016 presidential nominee. After befuddling his presidential primary opponents and political pundits of all stripes, Trump is now readying a general election campaign and preparing for a possible transition into the presidency.

Calif. customers see first BPA warning signs at checkouts

Businesses across California rolled out signs at checkout stands yesterday warning that certain food and beverage packaging contains harmful chemicals.

In San Francisco, a local business reported no trouble complying with the new state requirements about bisphenol A (BPA).

The Market, an upscale food court on the ground level of Twitter's headquarters in downtown San Francisco, displayed a small laminated sign on each cash register informing customers that BPA, found in food and beverage cans, lids, and bottle caps, is "known by the State of California to cause harm to the female reproductive system."

CHEMICAL WATCH ARTICLES

EU Commission proposes OELs for 13 carcinogens

Revision of carcinogens and mutagens Directive includes respirable crystalline silica

13 May 2016 / Europe, Occupational hygiene

The European Commission has proposed new occupational exposure limits (OELs) for 13

occupational carcinogens, including respirable crystalline silica.

The substances are among 20 priority chemical agents for which the Commission is conducting scientific and economic assessments. A second proposal covering the others will be issued by the end of the year, once further preparatory work is completed.

Speaking at a press conference in Brussels this morning, Marianne Thyssen – Commissioner for Employment, Social Affairs, Skills and Labour Mobility – said the proposal would save 100,000 lives in the next 50 years.

Cancer is responsible for half of all work-related deaths in the EU, but currently only three substances are subject to binding OELs under the carcinogens and mutagens Directive: benzene, hardwood dust and vinyl chloride monomer.

The proposal suggests lowering the OELs for hardwood dust and vinyl chloride monomer and creating OELs for a further 11, as follows:

- 1,2-epoxypropane; 2.4mg/m^3;
- 1,3-butadiene; 2.2mg/m^3;
- 2-nitropropane; 18mg/m^3;
- acrylamide; 0.1mg/m^3;
- bromoethylene; 4.4mg/m^3;
- chromium (VI) compounds; 0.025mg/m^3;
- ethylene oxide; 1,8mg/m^3;
- hardwood dusts; 3mg/m^3 (from7.77mg/m^3);
- hydrazine; 0.013mg/m^3;
- o-toluidine; 0.5mg/m^3;
- respirable crystalline silica (RCS); 0.1mg/m^3;
- refractory ceramic fibres (RCF); 0.3 fibres/ml; and
- vinyl chloride monomer (VCM); 2.6 mg/m^3 (from 5mg/m^3).

The proposals are unlikely, however, to satisfy trade unions. In March, the European Trade Union Institute (ETUI) called for binding OELs for 71 carcinogenic substances.

RCS is included as a 'process generated' substance. Silicosis and lung cancer caused by occupational exposure to RCS is a particular concern in the construction industry, which accounts for 70% of all exposed workers.

The proposed limit for RCS of 0.1mg/m^3 is the same as the current limit in force in the US. However, the Occupational Safety and Health Administration has proposed lowering this to 0.05mg/m^3 – sparking legal challenges from trade groups and worker unions.

Related Articles

- Trade union body wants EU-binding limits on 70 carcinogens
- Osha's new silica rule faces legal challenges

Further Information:

- Press release
- Memo

Echa round-up

12 May 2016 / Europe, Exposure monitoring & measurement

Guidance

Echa has sent a draft update of chapter R15 of its *Guidance on information requirements and chemical safety assessment* (IR&CSA) to the Competent Authorities for REACH and CLP (Caracal) for consultation. The chapter deals with consumer exposure assessment.

Agency Whit Monday closure

Echa has advised it will be closed on 16 May, so its tools REACH-IT, R4BP 3 and support services are not available that day.

The office reopens at 9am on 17 May.

The Pic submission tool, ePIC, remains available at all times.

Translations of tips for users of chemicals in the workplace

The short guide for users of chemicals in the workplace is available in 23 languages. It describes how to get the most from the classification and labelling information received in an easy-to-read style. It is linked to the downstream user web page.

Further Information:

- Guidance
- Echa closure
- Tips for users of chemicals in the workplace

Study for EP committee recommends further regulation of FCMs

Paper and board top priority, say stakeholders

12 May 2016 / Europe, Food contact, Food & drink

Luke Buxton

Europe desk editor

The legal framework, regulating food contact materials (FCMs) at EU level, is 'not complete' and specific measures should be brought into harmonise priority materials, according to a study commissioned by the European Parliament (EP)'s Environment Committee.

The study, produced by the European Parliamentary Research Service (EPRS), follows the committee's workshop in January on FCMs legislation, led by Environment Committee member Christel Schaldemose.

The committee is finalising its own report on the subject, and the EPRS report will feed into this process.

Many stakeholders, says the study, "see no alternative to EU-level harmonisation of FCMs". Issues identified include member states being able to adopt measures at national level, which, its says, could create internal market barriers, without necessarily securing FCM safety; increase compliance costs; reduce competitiveness and innovation; and delay market access for businesses

The study consulted member state competent authorities, businesses and trade bodies, the majority of which recommended paper and board as the number one FCM candidate to be regulated under EU law. This was followed by printing inks; silicones and coatings; and rubbers.

Currently only four FCMs, out of 17 for which specific safety requirements may be adopted, are subject to 'specific measures' and detailed harmonisation at EU level:

- plastics (including recycled plastics);
- ceramics;
- regenerated cellulose film; and
- active and intelligent materials

Stakeholders acknowledged full harmonisation is a 'time-consuming' process and, therefore, urged the adoption of specific measures for some of the materials listed in Annex 1 to the framework Regulation.

They recommend EU specific measures should establish a single standard for analytical testing methods, to ensure the relevant FCM is tested with the same method across the EU.

Suggested improvements of existing rules

Survey participants said that control activities are not carried out with the 'same intensity' across member states, with some stakeholders saying they are only carried out from "time to time" rather than regularly, as requested by law. Limited data on this point means further research would be justified, the study said.

Michael Warhurst, director of NGO ChemTrust, which is campaigning for greater regulation of FCMs and recently published a briefing on the subject, said: “It is unacceptable that FCMs do

not have proper EU regulation. The [European] Commission must acknowledge this policy area needs the resources necessary to develop and implement a regulatory system that protects the public, and addresses important issues like the use of recycled materials in food packaging."

Related Articles

- Lack of harmonised FCM regulation 'increasing compliance costs'

Further Information:

- EPRS study
- CHEM Trust briefing

House committee questions IRIS reforms

EPA programme 'suffers from lack of transparency', McCarthy told

12 May 2016 / United States, Risk assessment

Kelly Franklin

Editor, North America

In the latest chapter of the ongoing criticism of the EPA's Integrated Risk Information System (IRIS), the US House Committee on Science, Space and Technology has asked the agency to clarify how it has been reforming the programme.

A letter from committee chairman, Lamar Smith (R-Texas), to EPA Administrator, Gina McCarthy, on 10 May says IRIS "appears to suffer from a lack of transparency and an inability to produce work in a timely matter", and asks her to furnish information about the programme to "assist in the committee's oversight of this matter".

The committee received a briefing on IRIS from EPA staff on 27 April. But Mr Smith wrote that while this meeting was "helpful and appreciated", it did not answer all of its questions. This includes "details relating to some basic operating methods of the programme".

The EPA could not, for example, identify its policies on the identification and determination of substances to be assessed under the programme, he said.

It was also "unable to confirm which agency official, if any, holds the final decision-making power to determine whether an assessment is necessary".

Since 2008, the Government Accountability Office (GAO) has published three reports highlighting concerns with the IRIS programme. According to the letter, 12 of the 17 recommendations made by the investigative group remain unresolved.

The National Academy of Science (NAS) also provided recommendations for the programme in 2011, based on a review of the formaldehyde assessment process. But despite reiteration of these in 2014, not all of the improvements have been implemented, said the letter.

Mr Smith wrote that the committee is "concerned that EPA is not taking the recommendations of GAO and NAS seriously".

Like a similar letter issued to EPA by the House Committee on Oversight and Government Reform earlier this year, the committee points out that the agency has failed to develop a handbook to "develop clear and transparent processes" around the IRIS programme, as recommended by NAS.

It says that in the April briefing, the EPA "was unable to provide any clarity on the status or development" of this document.

The letter also pointed out that the EPA's decision to no longer announce availability of draft IRIS assessments in the *Federal Register* "appears to directly contradict specific recommendations for more transparency".

It has until 24 May to respond to the information request.

Politics driving decision making?

In a separate letter, Mr Smith asked Ms McCarthy about the EPA's apparent retraction of a final Cancer Assessment Review Committee (CARC) report for glyphosate.

According to the letter, the EPA apparently posted a final report indicating that the herbicide glyphosate is "not likely to be carcinogenic to humans", but has since said that the analysis was not final and that the document was posted "inadvertently".

This "backtracking on the finality of its own science review", Mr Smith wrote, "raises concerns about the agency's willingness to provide a fair assessment.

"That the EPA would remove a report, which was marked as a 'final report' and signed by thirteen scientists, appears to be yet another example of this agency's attempt to allow politics rather than science drive its decision making," he added.

Related Articles

- US EPA reports on IRIS improvements to Congress
- US GAO report criticises EPA IRIS programme
- US EPA's formaldehyde assessment not good enough, says National Academy of Sciences
- Report to US Congress finds 'substantial improvements' in IRIS
- House oversight committee to investigate IRIS programme
- US EPA stops posting IRIS consultations in Federal Register

Further Information:

- IRIS letter
- CARC letter

OTHER ARTICLES

Toxic Substance Control Act Under Reform

3BL Media (press release)

The **Toxic Substance** Control Act (1976) is currently the oldest piece of toxic legislation in the United States. The TSCA covers over 84,000 chemicals ...

Shimkus: **Toxic Substances** Deal 'Very Close,' But Not Finished

Morning Consult

Negotiations to update the **Toxic Substances** Control Act are touch and go, but House and Senate lawmakers say they are "very close" to a deal, Rep.

Chemicals Deal 'Very Close' But Not Yet Done: Shimkus - Bloomberg BNA

Full Coverage

Better to play in wet mud

Martha's Vineyard Times

Tire rubber contains many harmful chemicals, including styrene, butadiene, cadmium, and other **toxic chemicals**. Many of these are neurotoxic or ...

Lawmakers Aim for Deal on **Toxic Chemical** Regulations This Week

Morning Consult

Lawmakers and environmentalists are hopeful that a deal will be completed soon on regulating dangerous **chemicals**, now that California Sen.

Here's How to Detox Every Aspect of Your Life (and Your Home)

StyleCaster

There are a few simple things you can switch-up to avoid over-exposure to **toxic chemicals** every day, and to find out how we spoke with Sophia Ruan ...

To: Conger, Nick[Conger.Nick@epa.gov]
Cc: Harrison, Melissa[Harrison.Melissa@epa.gov]; Milbourn, Cathy[Milbourn.Cathy@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]
From: Jones, Jim
Sent: Tue 5/3/2016 1:25:34 PM
Subject: Re: Options on BNA story?

Ex. 5 - Deliberative Process

Sent from my iPhone

On May 3, 2016, at 9:10 AM, Conger, Nick <Conger.Nick@epa.gov> wrote:

Ex. 5 - Deliberative Process

Nick Conger

U.S. Environmental Protection Agency

Office: (202) 564-6287

Cell: (202) 412-2655

From: Harrison, Melissa
Sent: Tuesday, May 03, 2016 9:01 AM
To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Conger, Nick <Conger.Nick@epa.gov>
Cc: Jones, Jim <Jones.Jim@epa.gov>
Subject: Options on BNA story?

Ex. 5 - Deliberative Process

http://www.bna.com/epa-panel-finds-n57982070575/

EPA Panel Finds Glyphosate Not Likely to Cause Cancer

From Daily Environment Report™

By David Schultz

May 2 — Glyphosate, a weed killer developed by Monsanto that is now the most widely

used pesticide in the U.S., likely does not cause cancer, according to an Environmental Protection Agency review panel.

The EPA's Cancer Assessment Review Committee made the determination after analyzing several dozen published and unpublished scientific studies of the chemical. The committee finalized its report on Oct. 1, 2015, but did not release it to the public until late April, when the agency inadvertently posted the report online.

The report's findings disagree with a 2015 review of glyphosate by the World Health Organization's International Agency for Research on Cancer (IARC), which found that the pesticide is a "probable carcinogen" (59 DEN A-10, 3/27/15).

WHO's Findings Disputed

The EPA cancer review committee, led by staffers from the Health Effects Division of the agency's Office of Pesticide Programs, poked a number of holes in the methodology used by IARC for its review of glyphosate, which is the active ingredient in Monsanto's Roundup herbicide as well as hundreds of other products made by dozens of other companies.

For example, the EPA report noted that the IARC scientists disregarded several studies on the effects of exposure to glyphosate because these studies showed no positive results. The EPA report also said the studies IARC chose to include in its review had significant limitations.

Release of the IARC finding on glyphosate had serious negative consequences for the agricultural chemical industry.

It was the basis for a decision by California to require all products containing glyphosate to be listed as carcinogenic, a decision that Monsanto is challenging in court (173 DEN A-6, 9/8/15).

The IARC finding also led to numerous product liability lawsuits against Monsanto from people arguing that exposure to the company's pesticide was the cause of their illnesses (230 DEN A-9, 12/1/15).

Monsanto Statement

"No pesticide regulator in the world considers glyphosate to be a carcinogen, and this conclusion by the U.S. EPA once again reinforces this important fact," Monsanto CEO Hugh Grant said in a statement. "Unfortunately, last year's inconsistent classification by IARC generated unwarranted concern and confusion about this important agricultural tool."

The IARC did not immediately respond to requests from Bloomberg BNA for comment.

The EPA review committee's findings are part of a broader look by the agency at the overall health and environmental effects of glyphosate as a part of its registration review program, which conducts risk reviews of every pesticide chemical once every 15 years.

If the EPA determines that the science shows that the way glyphosate is being used now exceeds acceptable risks, it can enact use restrictions on the chemical or take it off the market altogether.

Report Posted April 29

The EPA posted the cancer review committee's report April 29, along with more than a dozen other glyphosate-related documents, to Regulations.gov, an online document repository for federal agencies.

Then, after the report had been widely spread on social media, the cancer review committee's report and the other documents were removed from the EPA website on the afternoon of May 2.

"Preliminary glyphosate documents were inadvertently posted to the Agency's docket," EPA spokeswoman Melissa Harrison told Bloomberg BNA via e-mail. "These documents have now been taken down because our assessment is not final."

Label Changes?

Some of the other documents the EPA briefly made public pertained to two meetings pesticide regulators held with Monsanto representatives in the year after the IARC review was published.

A slide presentation made at one of these meetings by Monsanto representatives indicated the company may be willing to make voluntary changes to the labels of its glyphosate products to address concerns that they're harming the habitats of certain pollinating insects, including the monarch butterfly.

This document, along with summaries of the discussions during the company's two meetings with EPA pesticide regulators, were among those removed from Regulations.gov.

To contact the reporter on this story: David Schultz in Washington atdschultz@bna.com

To contact the editor responsible for this story: Larry Pearl atlpearl@bna.com

For More Information

A copy of the EPA's Cancer Assessment Review Committee report on glyphosate is available at http://src.bna.com/eAi.

A brief summary of EPA's meeting March 30, 2015, with Monsanto representatives is available at http://src.bna.com/eBJ.

A brief summary of EPA's meeting June 4, 2015, with Monsanto representatives is available at http://src.bna.com/eBL.

A copy of the slide presentation Monsanto representatives made for EPA pesticide regulators last year is available athttp://src.bna.com/eBx.

Melissa J. Harrison

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To: Strauss, Linda[Strauss.Linda@epa.gov]
Cc: Wise, Louise[Wise.Louise@epa.gov]; Mojica, Andrea[Mojica.andrea@epa.gov]
From: Jones, Jim
Sent: Mon 5/2/2016 8:29:43 PM
Subject: Re: AWARENESS FW: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

Ex. 5 - Deliberative Process

Sent from my iPhone

On May 2, 2016, at 4:04 PM, Strauss, Linda <Strauss.Linda@epa.gov> wrote:

Outlets asking:

WSJ

Bloomberg

Bloomberg/BNA

Reuters Freelancer

Agi- pulse

Freelancer

From: Strauss, Linda
Sent: Monday, May 02, 2016 3:56 PM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Mojica, Andrea <Mojica.andrea@epa.gov>
Subject: AWARENESS FW: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer
Importance: High

Ex. 5 - Deliberative Process

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 3:39 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>

Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: FW: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

Ex. 5 - Deliberative Process

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 3:34 PM
To: Harrison, Melissa <Harrison.Melissa@epa.gov>; Conger, Nick <Conger.Nick@epa.gov>; Perry, Dale <Perry.Dale@epa.gov>
Cc: Hull, George <Hull.George@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

Ex. 5 - Deliberative Process

Outlets asking:

WSJ

Bloomberg

Bloomberg/BNA

Reuters Freelancer

Agi- pulse

Freelancer

http://biologicaldiversity.org/news/press_releases/2016/glyphosate-05-02-2016.html

For Immediate Release, May 2, 2016

Contact: Nathan Donley, (971) 717-6406, ndonley@biologicaldiversity.org

EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause

Cancer

PORTLAND, *Ore.*— An EPA analysis relying heavily on unpublished, industry funded studies has determined that glyphosate, commonly known as Roundup, is "not likely to be carcinogenic to humans." The EPA determination, released to the public on Friday, stands in sharp contrast to a finding last year by the World Health Organization's cancer-research arm that glyphosate is a probable human carcinogen.

"EPA's determination that glyphosate is non-carcinogenic is disappointing, but not terribly surprising — industry has been manipulating this process for years," said Nathan Donley, a scientist with the Center for Biological Diversity. "The analysis done by the World Health Organization is more open and transparent and remains the gold standard."

The EPA's analysis relied heavily on industry-funded studies that have not undergone public scrutiny, while the WHO used publically available research for its analysis. Furthermore, the WHO took into account studies on actual products that are available on store shelves, while the EPA ignored those studies to focus solely on studies that tested glyphosate as a single ingredient. Most products containing glyphosate have other ingredients that can make the pesticide more dangerous.

"We shouldn't gamble with the risk of cancer and must take appropriate precautions until we get a conclusive answer about the true dangers of glyphosate," said Donley. "The indiscriminate drenching of farms, ball fields and backyards with glyphosate needs to end."

The EPA's industry-friendly determination comes amid a fierce debate in Europe and the United States over the safety of glyphosate.

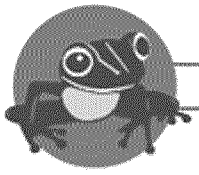
In February 35 members of the U.S. House of Representatives sent a letter to EPA Administrator Gina McCarthy expressing concerns regarding the potential negative health and environmental impacts of a pesticide, Enlist Duo, that combines glyphosate and 2,4-D. The agency is currently reanalyzing its decision to register the dangerous pesticide after it was revealed that the industry had withheld data on how the pesticides work in combination with other ingredients to have a stronger effect on the environment.

This finding comes as the EPA is in undertaking a "registration review" of glyphosate, a process designed to determine whether the chemical can safely be used in light of new scientific research. These documents will inform the agency's decision on whether to allow glyphosate to be used for the next 15 years. The last time the EPA fully analyzed the threats posed by glyphosate was 1993.

The Center for Biological Diversity is a national, nonprofit conservation organization with more than 1 million members and online activists dedicated to the protection of endangered species and wild places.

Alaska . Arizona . California . Florida . Minnesota . Nevada . New Mexico . New York . Oregon . Vermont . Was

P.O. Box 710 . Tucson, AZ 85702-0710 *tel:* (520) 623.5252 *fax:* (520) 623.9797 *www.BiologicalD*



CENTER *for* BIOLOGICAL DIVERSITY *Because life is good.*

From: Jones, Tawaunna
Location: C East3130A WJC East
Importance: Normal
Subject: Items related to Glyphosate and Dicamba (Jim you can call Michael on Ex. 6 - Personal Privacy
Start Date/Time: Mon 11/16/2015 8:00:00 PM
End Date/Time: Mon 11/16/2015 8:30:00 PM

Good Morning Mr. Dykes,

Mr. Jones has to re-schedule your meeting until next week. I am sorry for the short notice.

Thank you,
Tawaunna Jones

Tawaunna
I just talked with you to schedule time to meet with Jim Jones and you asked that I send you an email so you open his schedule.

I have worked with Gloria in the past to schedule 30 minute one on one meetings with Jim to discuss various issues pending in Jim's department at the EPA. I would like to schedule another one of those 30 minutes one on one discussions with Jim to discuss a couple of items related to glyphosate and dicamba this week if it would work with Jim's schedule. Please give me a call to discuss specific times that may work.

Thank you
Michael Dykes DVM
Monsanto Company
VP Government Affairs
1300 Eye Street NW
Washington, DC 20005
Office 202-257-1688
Cell 202-257-1688

To: Keigwin, Richard[Keigwin.Richard@epa.gov]
Cc: Housenger, Jack[Housenger.Jack@epa.gov]; Mojica, Andrea[Mojica.andrea@epa.gov]; Wise, Louise[Wise.Louise@epa.gov]; Perlis, Robert[Perlis.Robert@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]; Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Sisco, Debby[Sisco.Debby@epa.gov]
From: Jones, Jim
Sent: Tue 5/10/2016 4:15:28 PM
Subject: Re: glyphosate draft response for review

Thx Rick. Jim

Sent from my iPhone

On May 10, 2016, at 10:48 AM, Keigwin, Richard <Keigwin.Richard@epa.gov> wrote:

Ex. 5 - Deliberative Process

From: Housenger, Jack
Sent: Tuesday, May 10, 2016 10:45 AM
To: Mojica, Andrea <Mojica.andrea@epa.gov>; Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: RE: glyphosate draft response for review

A few comments

From: Mojica, Andrea
Sent: Tuesday, May 10, 2016 10:32 AM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Housenger, Jack <Housenger.Jack@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: glyphosate draft response for review

All,

Attached is a draft response to Chairman Lamar Smith's (Committee on Science, Space, and Technology) glyphosate inquiry. I have attached in the incoming letter to the Administrator as well. Please let me know if you have any comments by May 12th.

Thanks,

Andrea

To: Jim Jones[jjones4411@gmail.com]
From: Jones, Jim
Sent: Sun 11/29/2015 7:08:39 PM
Subject: Fwd: materials for Tom B glyphosate meeting
417300_2015-10-01_TXR0057299.pdf
ATT00001.htm
TB Brief Glyphosate JR 11 3 15.pptx
ATT00002.htm

Sent from my iPhone

Begin forwarded message:

From: "Mojica, Andrea" <Mojica.andrea@epa.gov>
To: "Jones, Jim" <Jones.Jim@epa.gov>, "Wise, Louise" <Wise.Louise@epa.gov>
Subject: materials for Tom B glyphosate meeting

Jim,

Attached are the materials for the Tom B glyphosate briefing. The relevant cancer slides from your briefing last week and the glyphosate CARC document from October 1, 2015. OK to send to ORD?

Thanks,

Andrea

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **October 1, 2015**

SUBJECT: **GLYPHOSATE:** Report of the Cancer Assessment Review Committee

PC Code: 417300	**DP Barcode:** N/A
Decision No.: N/A	**Registration No.:** N/A
Petition No.: N/A	**Regulatory Action:** N/A
Risk Assessment Type: NA	**Case No.:** N/A
TXR No.: 0057299	**CAS No.:** 1071-83-6
MRID No.: N/A	**40 CFR:** N/A

FROM: Jess Rowland,
Deputy Division Director
Chair, Cancer Assessment Review Committee
And
Karlyn Middleton, Co-Chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Charles Smith, Chief,
Risk Assessment Branch I
Health Effects Division (7509P)
And
Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division

On September 16, 2015, the Cancer Assessment Review Committee (CARC) of the Health Effects Division, of the Office of Pesticide Programs evaluated the carcinogenic potential of Glyphosate in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
Glyphosate

FINAL REPORT
October 1, 2015

CANCER **A**SSESSMENT **R**EVIEW **C**OMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S Environmental Protection Agency

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COMMITTEE MEMBERS IN ATTENDANCE:

Jess Rowland, M.S., Chair

Karlyn Middleton, M.S., Co-Chair

Gregory Akerman, Ph.D.

Lori Brunsman, B.S.

Jonathan Chen, Ph.D.

Anwar Dunbar, Ph.D.

Ray Kent, Ph.D.

Jessica Kidwell, M.S.

John Liccione, Ph.D.

Dannelle Lobdell, Ph.D., Epidemiologist, ORD

Nancy McCarroll, M.S.

Chris Schlosser, M.S.

Charles Wood D.V.M., Ph.D., Pathologist, ORD

EXECUTIVE SUMMARY

Glyphosate is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops.

In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division (HED), of the Office of Pesticide Programs (OPP), of the U.S. Environmental Protection Agency (USEPA) evaluated the carcinogenic potential of glyphosate. In accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* the CPRC classified glyphosate as a Group E Chemical: "Evidence of Non-Carcinogenicity for Humans" based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR# 0008897).

Earlier this year (March 2015), the International Agency for Research on Cancer (IARC), Lyon, France, assessed the carcinogenic potential of glyphosate. The IARC reviewed the available epidemiological studies and carcinogenicity studies for glyphosate in experimental animals. The IARC concluded that there is *limited evidence* in humans for the carcinogenicity of glyphosate based on a positive association for non-Hodgkin lymphoma (NHL). The IARC also concluded that there is *sufficient evidence* in experimental animals based on significant positive trends for kidney tumors in one study and for hemangiosarcomas in another study in male mice. IARC determined that there is strong evidence for genotoxicity. Overall, IARC classified glyphosate as "*probably carcinogenic to humans (Group 2A)* (IARC, 2015).

IARC's conclusion was based on epidemiologic studies available in the open literature and carcinogenicity studies in rats (4 studies) and mice (2 studies) by dietary administration. Of these six studies reviewed by IARC, two studies in rats and one study in mice were previously not available to OPP. The conclusion by IARC and the additional studies not available to OPP, prompted the agency to re-evaluate the carcinogenic potential of glyphosate.

On September 16, 2015, HED's Cancer Assessment Review Committee (CARC) evaluated all available epidemiological studies published in the open literature that examined the association between glyphosate exposure and one or more cancer outcomes. This included one cohort study, seven nested case-control studies based on the cohort study population, and 25 case- control studies. The CARC also evaluated 11 chronic toxicity/carcinogenicity studies in rats (7) and mice (4) following dietary administration for up to two years. Six of the studies (4 rat and 2 mouse) were submitted to OPP to support registration/re-registration requirements, including two studies in rats and one study in mice which were not previously available to OPP (but reviewed by IARC). Data for review of the other five studies (3 rat and 2 mouse) were obtained from a review article and its supplement published in the open literature (Greim *et al.,* 2015) that also had not been previously reviewed by the agency (IARC did not evaluate the five studies cited in the Greim *et al.* 2015 review article). The CARC also evaluated the mutagenicity/genotoxicity studies submitted to OPP as well as studies summarized in two review articles (Williams *et al*., 2000, and Kier and Kirkland, 2013) published in the open literature.

The CARC concluded that the epidemiological studies in humans showed no association between glyphosate exposure and cancer of the following: oral cavity, esophagus, stomach, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, brain (gliomas), soft-tissue sarcoma, leukemia, or multiple myelomas.

The CARC concluded that there is conflicting evidence for the association between glyphosate exposure and NHL. No association between glyphosate exposure and NHL was found in population-based case-control studies in the United States, Canada or France. Additionally, the large prospective Agricultural Health Study (AHS) with 54,315 licensed pesticide applicators in Iowa and North Carolina did not show a significantly increased risk of NHL. A population-based case-control study from Sweden suggested an association between glyphosate exposure and NHL; however, this finding was based on only 4 glyphosate-exposed cases and 3 controls.

When data from two case-control studies in Sweden (one on NHL and the other on hairy cell leukemia) were pooled, a univariate analysis showed an increased risk (odds ratio (OR) = 3.04; 95% confidence interval (CI) = 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, the risk was attenuated (OR=1.85; 95% CI=0.55–6.20). In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analysis showed an increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51). A meta-analysis of the six separate studies showed an association between glyphosate exposure and NHL with a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014). The CARC noted that most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and had risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data.

In an attempt to address the noted power/sample size issues across studies, IARC used adjusted weighting estimates of the two Swedish studies (Hardell *et al*. 2002 and Eriksson *et al*. 2008) and

reported an lower odds ratio in a second meta-analysis of the same data (OR=1.3; 95% CI=1.03–1.65). Given the limitations of the studies used and uncertainty in the analytical methods, the CARC concluded that a different weighting scheme could have resulted in a different meta risk ratio. Thus, while epidemiologic literature to date does not support a direct causal association, the CARC recommends that the literature should continue to be monitored for studies related to glyphosate and risk of NHL.

Overall, the CARC concluded that there was no evidence of carcinogenicity in the eleven carcinogenicity studies conducted in Sprague Dawley or Wistar rats and CD-1 mice. There were no treatment-related increases in the occurrence of any tumor type in either sex of either species.

By contrast, the IARC concluded that there is *sufficient evidence* in experimental animals based on a positive trend in the incidence of a relatively rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in CD-1 males in one feeding study. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. The CARC did not consider these tumors to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported non-neoplastic changes, were not statistically significant on pairwise analysis with concurrent control groups, and/or were within the range of the historical control data. If the kidney tumors and the hemangiosarcomas are really treatment-related, it is unlikely that the same tumors would not have been detected at higher incidences in the studies in the other studies of CD-1 mice when tested at similar or higher doses (1000–4000 mg/kg/day). Moreover, in 4 of the 11 studies (3 rat and 1 mouse) evaluated by CARC, there was no biologically or statistically significant increases in the occurrence of any tumor type in either species. The other observed differences in incidence did not show a dose response relationship, and were within the range of the background/historical control range. The four studies which were negative for carcinogenicity were reported in the review article by Greim *et al.* (2015) but were not included in the IARC evaluation. This omission of the negative findings from reliable studies may have had a significant bearing on the conclusion drawn for evidence of carcinogenicity in animals.

The CARC evaluated a total of 54 mutagenicity/genotoxicity studies which included studies submitted to the agency, as well as studies reported in the two review articles (Williams *et al.*, 2000, and Kier and Kirkland, 2013). A number of studies reported in the review article by Kier and Kirkland (2013) were not considered by IARC. The CARC, based on a weight-of-evidence of the *in vitro* and *in vivo* studies, concluded that there is no concern for genotoxicity or mutagenicity. Glyphosate was no mutagenic in bacterial reversion (Ames) assays or *in vitro* mammalian gene mutation assays. There is no convincing evidence that glyphosate induces micronuclei formation or chromosomal aberrations *in vitro* or *in vivo*.

By contrast, IARC's conclusion that glyphosate is genotoxic based on positive results that included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e.*, no purity information was provided). The IARC analysis also focused on DNA damage as an endpoint (*e.g.*, comet assay). DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA

changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited as positive findings for chromosomal damage had deficiencies in the design and/or conduct of the studies confounding the interpretation of the results. In addition these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. Furthermore, IARC's evaluation did not include a number of negative results from studies that were reported in the review article by Kier and Kirkland (2013). The inclusion of the positive findings from studies with known limitations, the lack of reproducible positive findings and the omission of the negative findings from reliable studies may have had a significant bearing on IARC's conclusion on the genotoxic potential of glyphosate.

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, based on the weight-of-evidence, glyphosate is classified as "Not Likely to be Carcinogenic to Humans". This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk/odd ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis with concurrent control groups, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

I. INTRODUCTION

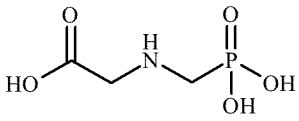
On September 16, 2015 the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of glyphosate.

II. BACKGROUND INFORMATION

Glyphosate (*N*-(phosphonomethyl) glycine) is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops. Tolerances are currently established for residues of glyphosate in/on various plant commodities at 0.2–400 ppm (40 CFR §180.364 (a)) (1). Registered uses range from tree nuts, citrus, and grapes to corn, soybeans, cotton, and rice. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Aquatic and terrestrial registered uses of glyphosate include non-selective control of nuisance aquatic weeds, ornamentals, greenhouses, residential areas, ornamental lawns and turf, fallow land, pastures, and nonagricultural rights-of-way.

The chemical structure and nomenclature for glyphosate is presented in Table 1.

Table 1. Chemical Nomenclature of Glyphosate

Compound	
Common name	Glyphosate
Company experimental name	DPX-B2856
IUPAC/CAS name	*N*-(phosphonomethyl)glycine
CAS registry number	1071-83-6

Glyphosate is formulated in liquid and solid forms, and it is applied using ground and aerial equipment. Application rates of glyphosate to food crops range from <1 pound (lb) of acid equivalent (ae) per acre (A) for a variety of crops to approximately 15 lb ae/A for spray and spot treatments of crops including tree nuts, apples, citrus, and peaches. Residential lawn and turf application rates range from <1 lb ae/A to approximately 10.5 lb ae/A. The application timing of glyphosate is varied. Glyphosate can be applied early and late in the season, at pre-plant, planting, pre-emergence, pre-bloom, bud stage, pre-transplant, pre-harvest, post-plant, post-transplant, post-bloom, and post-harvest. It can also be applied during dormant stages and to fallow land, established plantings, stubble, and when needed. In September 1993, the agency issued the glyphosate Reregistration Eligibility Decision (RED) document (D362745), available from http://www.epa.gov/pesticides/reregistration/REDs/old_reds/glyphosate.pdf.

In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division, Office of Pesticide Programs, in accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* classified glyphosate as a Group E Chemical: Evidence of Non-Carcinogenicity for Humans. This classification was based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR No. 0008897).

In 2002, the European Union (EU) concluded that there was no evidence of carcinogenicity for glyphosate in long-term studies with mice and rats (EU, 2002).

In 2004, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that there was no evidence of carcinogenicity for glyphosate in long term studies in mice and rats and there was no evidence for genotoxic potential (JMPR, 2004).

In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as a Group 2A chemical (Probable Human Carcinogen) based on *limited evidence* of carcinogenicity in humans and sufficient evidence in experimental animals. The limited evidence in humans was based on a positive association between non-Hodgkin lymphoma (NHL) and glyphosate exposure from published epidemiology studies. The *sufficient evidence* in experimental animals was based on a positive trend in the incidence of renal tubular carcinoma and renal tubule adenoma/ carcinoma combined in male CD-1 mice in one study and on a positive trend in the incidence of hemangiosarcomas in male CD-1 mice in another study. There is strong evidence that glyphosate causes genotoxicity (IARC, 2015).

In 2015, two chronic toxicity/carcinogenicity studies in rats (MRID Nos. 49631701; 4970460) and one carcinogenicity study in mice (MRID No. 49631702) that were reviewed by IARC, but not previously available to OPP, were submitted and reviewed. This assessment by the CARC includes all of the studies (epidemiology and animals) reviewed by IARC as well as a subset of animal studies reported in a review article by Greim *et al.* (2015) but not reviewed by IARC.

III. EPIDEMIOLOGY

This section includes a review of epidemiologic cohort and case-control studies of glyphosate to evaluate whether exposure to glyphosate is associated causally with the risk of developing cancer in humans.

The Agricultural Health Study (AHS) is a large prospective study conducted in Iowa and North Carolina. Participants (private and commercial applicators) were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying pesticides (including glyphosate), and frequency (days of use per year) and duration (years of use) of pesticide use. Data on the use of personal protective equipment, other farming practices, dietary and lifestyle information, demographic data, and medical information were also collected via the questionnaire (Alavanja *et al.,* 1996). The role of pesticide use and lymph hematopoietic cancers, and in particular NHL, has been studied in several investigations. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available (De Roos *et al.*, 2005); however, for NHL and other non-solid tumors, several investigations are published.

A. Cohort Study

There are multiple published studies which use data from the same cohort, the AHS (Alavanja *et al.,* 2003; Flower *et al.*, 2004; De Roos *et al.*, 2005; Engel *et al.*, 2005; Lee *et al.*, 2007; Landgren *et al.*, 2009; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010). It should be noted that there is some overlap between the cases and person-time reported findings in the AHS.

B. Case-Control Studies

Three case-control studies conducted by the National Cancer Institute in Iowa and Minnesota during the 1980s were reported by Brown *et al.* (1990), Cantor *et al.* (1992) and Brown *et al.* (1993).

De Roos *et al.* (2003) and Lee *et al.* (2004a) reported the results of case-control studies conducted in Iowa, Minnesota, Nebraska and/or Kansas in the U.S.A.

The Canadian population based case-control studies were reported by McDuffie *et al.*, 2001; Hohenadel *et al.*, 2011; Karunanayke *et al.*, 2012; and Kachuri *et al.*, 2013.

Results of the Swedish case-control studies were reported by Nordstrom *et al.*, 1998; Hardell and Erikson, 1999 and Hardell *et al.*, 2002; and Eriksson *et al.*, 2008.

A single case-control study conducted in France was reported by Orsi *et al.* (2009).

Coco *et al.*, (2013) reported the results of a pooled analyses of case-control studies conducted in six European countries between 1998 and 2004.

Case-control studies on the cancer of the brain (mainly gliomas) were reported by Ruder *et al.* 2004; Carreon *et al.*, 2005; Lee *et al.*, 2005; and Yiin *et al.*, 2012.

Case-control studies on other cancer sites were reported by Alavanja *et al.*, 2004 (lung); Bank *et al.*, 2011 and Koutros *et al.*, 2013 (prostate); Pahwa *et al.*, 2012 (soft tissue sarcoma) and Lee *et al.,* 2004b (stomach and esophagus).

Schinasi and Leon (2014) conducted a meta-analysis of the six studies that evaluated NHL and glyphosate exposure (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; DeRoos *et al.*, 2003; 2005; Eriksson *et al.*, 2008; and Orsi *et al.*, 2009). Sorahan (2015) conducted a re-analysis of the multiple myeloma in the U.S. AHS.

C. Results

A summary of the studies evaluating the association between glyphosate exposure and cancer are discussed below.

- Results of the studies reporting data on solid tumors (non-lymphohematopoietic) at various anatomical sites are presented in Table 2.

- Results of the studies reporting data on glyphosate exposure and non-solid tumors (lymphohematopoietic) are presented in Table 3.

1. Solid Tumor Cancer Studies

Within the AHS study cohort, a number of authors evaluated several anatomical cancer sites in relation to pesticide use. A discussion of studies outside of the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in Section C.2. (Non-Solid Tumor Sites).

(i) Cancer at Multiple Sites

De Roos *et al.*, (2005) evaluated associations between glyphosate exposure and cancer incidence in the AHS cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. The authors used Poisson regression to estimate exposure-response relationships between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Exposure to glyphosate was not associated with all cancers combined [Rate Ratio (RR) =1.0 with 95% Confidence Interval (CI) of 0.90–1.2)] or any cancer at a specific anatomical site.

Several AHS nested case-control analyses as well as the cohort analysis from De Roos *et al.*, 2005, also provide information concerning the carcinogenic potential of glyphosate. As presented in Table 2, there is no statistical evidence of an association with glyphosate presented across these studies. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and cancers of the oral cavity (De Roos *et al.*, 2005), colon (De Roos *et al.*, 2005; Lee *et al.*, 2007), rectum (De Roos *et al.*, 2005; Lee *et al.*, 2007), lung (De Roos *et al.*, 2005), kidney (De Roos *et al.*, 2005), bladder (De Roos *et al.*, 2005), pancreas (De Roos *et al.*, 2005; Andreotti *et al.*, 2009), breast (Engel *et al.*, 2005), prostate (Alavanja *et al.*, 2003; Koutros *et al.*, 2013) or melanoma (De Roos *et al.*, 2005; Dennis *et al.*, 2010). The risk ratios (OR) or rate ratios (RR) and 95% confidence interval (CI) for these studies are provided in Table 2.

In a population-based study (Band *et al.*, 2011) outside of the AHS, Canadian researchers reported non-significantly elevated odds of prostate cancer in relation to glyphosate use (OR=1.36; 95% CI=0.83–2.25). This study included prostate cancer cases from 1983-1990, prior to the prostate-specific antigen (PSA) era. Consequently, the study included more advanced tumors before diagnosis. Additionally, these data are in conflict with the results of Alavanja *et al.* (2003), which reflects the PSA-era cases (*i.e.*, cases which are typically identified at an earlier stage in the progression of the disease). Koutros *et al.* (2013) did not identify an association with advanced prostate cancer (OR=0.93; 95% CI=0.73–1.18) in a prostate cancer follow-up study within the AHS.

A Canadian case-control study (Pahwa *et al.*, 2011) examined exposure to pesticides and soft tissue sarcoma and found no relation with the use of glyphosate (OR=0.90; 95% CI= 0.58–1.40).

Flower *et al.* (2004) examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with maternal use exposure to glyphosate (OR=0.61; 95% CI= 0.32–1.16) or paternal (prenatal) exposure to glyphosate: (OR=0.84; 95% CI= 0.35– 2.54).

(ii) Brain (Glioma) Cancer

Lee *et al.* (2005) investigated the association between brain cancer with farming and agricultural pesticide use. The authors conducted telephone interviews of men and women diagnosed with gliomas (n=251) between 1988 and 1993 in Nebraska and in controls (n=498) identified from the same regions. Matching for age and vital status, study authors reported a non-significant elevated odds of glioma (OR=1.5; 95% CI=0.7–3.1) in relation to glyphosate use; however, the results were significantly different between those who self-reported pesticide use (OR=0.4; 95% CI=0.1–1.6), and for those for whom a proxy respondent was used (OR=3.1; 95% CI=1.2–8.2), indicating recall bias was likely a characteristic of this study.

Three population-based case-control studies evaluated the risk of brain cancer, specifically, glioma risk, among men and women participating in the Upper Midwest Health Study (Carreon *et al.*, 2005; Ruder *et al.*, 2004; Yiin *et al.*, 2012). Ruder *et al.* (2004) reported no association between brain cancer and glyphosate use, but did not present any specific results (*i.e.* quantitative data). Among glioma cases identified 1995–1997 by Carreon *et al.* (2005), the authors found little evidence of a role for glyphosate in the etiology of this tumor. Herbicide use, including glyphosate was not associated with glioma in women by proxy respondents (OR=0.75; 95% CI=0.4–1.3) or excluding proxy respondents (OR=0.6; 95% CI=0.3–1.2). In the study by Carreon *et al.* (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to Lee *et al.* (2005). Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), the authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (home and garden use: OR=0.98; 95% CI=0.67–1.43; non-farm jobs: OR=0.83; 95% CI=0.39–1.73) (Yiin *et al.*, 2012).

(iii) Stomach and Esophageal Cancers

In a population-based case control study in eastern Nebraska, Lee *et al.* (2004) investigated pesticide use and stomach and esophageal adenocarcinomas. Cancer cases (stomach=170 and esophagus=137) were identified through the state cancer registry, and confirmed by a pathologist. The exposure assessment was based on self-reported pesticide use, with follow-up telephone interview to verify the reported information. There was no association between glyphosate exposure and either stomach cancer (OR=0.8; 95% CI=0.4–1.5) or esophageal cancer (OR=0.7; 95% CI=0.3–1.4).

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Cancer at Multiple Sites					
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	All cancers RR =1.0 (0.9-1.2)	No association between glyphosate exposure and all cancer including NHL	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)
Site-Specific Cancers: Lung; Oral cavity; Colon; Rectum; Kidney; Bladder; Prostate and Melanoma					
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	Lung RR= 0.9 (0.6-1.3) Oral Cavity RR=1.0 (0.5-1.8) Colon RR=1.4 (0.8-2.2) Rectum RR=1.3 (0.7-2.3) Pancreas RR=0.7 (0.3-2.0) Kidney RR=1.6 (0.7-3.8) Bladder RR=1.5 (0.7-3.2) Prostate RR=1.1 (0.9-1.3) Melanoma RR=1.6 (0.8-3.0)	No significant association between glyphosate exposure and cancer of the lung, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate or melanomas	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Breast Cancer					
Engel *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 30,454 wives of licensed pesticide applicators with no history of breast cancer at enrollment	Self-report questionnaire	Direct exposure (wives who applied) OR=0.9 (0.7-1.1) (Exposed: 82 cases, 10,016 controls) Indirect exposure (wives whose husbands applied) OR=1.3 (0.8-1.9) (Exposed: 109 cases, 9,304 controls)	No association between glyphosate exposure and breast cancer	Age, race and state of residence (Iowa and North Carolina). Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Pancreatic Cancer					
Andreotti *et al.* (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; follow-up to 2004 93 cases 82,503 controls	Self-report questionnaire; validated, reliability tested	Ever-use OR=1.1 (0.6, 1.7) (Exposed: 55 cases)	No association between glyphosate exposure and pancreatic cancer	Age, smoke, diabetes, applicator type. Limited to licensed applicators. Potential exposure to multiple pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Prostate Cancer					
Alavanja *et al.* (2003) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; cancer thru 1999 55,332 male applicators	Self-report questionnaire; validated, reliability tested	No quantitative risk estimate reported	No quantitative estimate due to lack of significant exposure-response association with prostate cancer.	Age, family history. Limited to licensed applicators. Potential exposure to multiple pesticides
Band *et al.* (2011) British Columbia, Canada	Case-Control 1983- 1990 1,516 prostate cancer patients 4,994 age-matched controls	Job exposure matrix for agriculture; detailed occupational history; exposure aggregated over all jobs reported. 60 exposed cases	OR=1.36 (0.83-2.25) (Exposed: 25 cases 60 controls)	No association between glyphosate exposure and prostate cancer	Alcohol consumption, cigarette years, education level, pipe smoking years and respondent
Koutros *et al.* (2013) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2003 1,962 incident cases, including 919 aggressive prostate cancers among 54,412 applicators	Self-report questionnaire, validated	OR=0.93 (0.73-1.18)	No association between glyphosate exposure and prostate cancer	Age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Colorectal Cancer					
Lee *et al*. (2007) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-97; follow-up to 2002 56,813 licensed pesticide applicators	Self-report questionnaire	Colon OR=1.0 (0.7-1.5) (Exposed: 151 cases 49 controls) Rectum OR=1.6 (0.9-2.9) (Exposed: 74 cases 18, controls) Colorectal OR=1.2 (0.9-1.6) (Exposed: 225 cases 67 controls)	No significant association between glyphosate exposure and colon, rectum or colorectal cancer	Age, smoking, state, total days use pesticides. Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Cutaneous Melanoma					
Dennis *et al.* (2010) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 150 cases, 24,554 non-cases	AHS self-report questionnaire	No quantitative risk estimate reported	No quantitative estimate due to lack of an association with cutaneous melanoma	Age, sex, tendency to burn, red hair, sun exposure time, BMI at 20 years

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Soft Tissue Sarcoma					
Pahwa *et al.* (2011) Canada	Case-Control 1991-1994 342 cases, 1506 age/resident matched controls	Self-reported use, structured interview/ questionnaire; cumulative exposure (+/-10 days/yr)	OR=0.90 (0.58-1.40)	No association between glyphosate exposure and soft tissue sarcoma	Significant medical history variables and with strata for the variables of age group and province of residence
Total Childhood Cancer					
Flower *et al.* (2004) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control; hybrid prospective/ retrospective 1993-1998 21, 375 children of licensed pesticide applicators In Iowa (n=17,357) North Carolina (n=4018)	Self-report questionnaire; duration and frequency of pesticide use; Female Family questionnaire (child name)	<u>Maternal use</u> OR=0.61 (0.32-1.16) 32 cases <u>Paternal use (prenatal)</u> OR=0.84 (0.35-2.34);	No association was detected between frequency of parental pesticide application of glyphosate and childhood cancer risk.	Potential exposure to other pesticides. Child age in multiple logistic [standardized incidence ratio (SIR)] was unadjusted

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Brain Cancer (Glioma)					
Lee *et al.* (2005a) Nebraska	Population based Case-Control study 1988-1993; 251 glioma cases 498 controls	Self-reported questionnaire information, telephone follow-up for unclear responses; men and women assessed separately	Self-Report OR=0.4 (0.1- 1.6) (Exposed: 4 cases 17 controls) Overall OR=1.5 (0.7-3.1) (Exposed: 17 cases 32 controls) Proxy report OR=3.1 (1.2- 8.2) (Exposed:13 cases 15 controls)	Non-significant excess risk for the overall group, but inconsistent for self-report and proxy indicating recall bias	Age, proxy, respond type
Ruder *et al.* (2004) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin, U.S.A.)	Population-based Case-Control 1995-1997 457 glioma cases 648 population controls	Self-report questionnaire, with telephone based follow-up	No quantitative risk estimate reported for glyphosate.	No association with glyphosate exposure and brain cancer	Farm residence, age, use of other pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Carreon *et al.* (2005) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 341 glioma cases, 528 controls	Self-report questionnaire	Proxy respondents OR=0.75 (0.4-1.3) (Exposed: 18 cases 41 Controls) Excluding proxy OR=0.6 (0.3-1.2) (Exposed:10 cases)	No association with glyphosate exposure and brain cancer	Age, education and use of other pesticide
Yin et al. (2012) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 798 glioma cases 1,175 controls	Self-report questionnaire	Home/garden use OR=0.98; 95% CI=0.67 - 1.43; Non-farm jobs: OR=0.83; 95% CI=0.39-1.73)	No significant positive association with glyphosate exposure and brain cancer	Age, sex, education and use of other pesticide

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Esophagus and Stomach Cancer					
Lee *et al*. (2004b) Nebraska, U.S.A.	Population based Case-Control 1988-1993 137 esophageal cases; 170 stomach cases; 502 controls	Self-report pesticide use, telephone structured interview	Esophagus OR=0.7 (0.3-1.4) (Exposed:12 cases 46 controls) Stomach OR=0.8 (0.4-1.5) (Exposed: 12 cases 46 controls)	No association with glyphosate exposure and esophagus or stomach cancer	Age, sex

2. Non-Solid Tumor Cancer Sites

A number of studies evaluating the possible link between pesticide use and lymphohematopoietic cancers such as leukemia, multiple myeloma and NHL are presented in Table 3.

(i) Leukemia

In a population-based case-control study in Iowa and Minnesota, Brown *et al.* (1990) investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR=0.9; 95% CI=0.5–1.6). The study population (578 cases; 340 living and 238 deceased and 1245 controls) was identified from cancers reported to state registry or authorities in 1981–1984, and the pesticide exposure assessment was performed through in-person interviews which the authors state likely reduced the exposure misclassification (*i.e.* incorrect exposure information). Although the large sample size is a strength of this study, the limitations include not controlling for exposure to other pesticides, limited power for studying the effects of glyphosate use, and the potential for recall bias.

In a Swedish population-based case-control study, 121 cases in men and 484 controls matched for age and sex were identified in 1987–1992 through the Swedish cancer registry. The authors reported a non-statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR=3.1; 95% CI=0.8–12.0), controlling for age, sex, and residential location. However, because these results are based on only 4 glyphosate-exposed cases and 5 exposed controls as noted by the authors, this risk should be interpreted with caution. Also, there was limited power to detect an effect and there was no adjustment for other exposures. At this time, there is limited available literature concerning glyphosate use and leukemia (Nordstrom *et al.*, 1998).

(ii) Multiple Myeloma

In a follow-up analyses using the same study population from Iowa and Minnesota Brown *et al.* (1993) investigated whether pesticide use is also related to multiple myeloma. Among men in Iowa (173 cases, 605 controls), the authors observed a statistically non-significant elevated association with glyphosate use (OR=1.7; 95% CI=0.8–3.6). However, the authors caution that while the study may lend support to the role of pesticides in general, the study limitations preclude use of the evidence as a definitive finding for any one compound.

De Roos *et al.* (2005) reported a suggestive association between multiple myeloma and glyphosate-exposed pesticide applicators based on a small number (32) of cases. For applicators with the full data set (54,315) and without adjustment for other variables the OR was 1.1; 95% CI=0.5–2.4. In the fully adjusted model, there was a non-statistically significantly elevated risk (OR=2.6; 95% CI=0.7–9.4), however, the number of participants included in this analysis was lower (n=40,716) due to missing data for the covariates. The authors postulated that the increased myeloma risk could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses.

Sorahan (2015), using Poisson regression, re-analyzed the AHS data reported by De Roos *et al.* (2005) to examine the reason for the disparate findings in relation to the use of a full data set versus the restricted data set. Risk ratios were calculated for exposed and non-exposed subjects. When adjusted for age and sex, the OR was 1.12 with the 95% CI of 0.5–2.49 for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of other pesticides did not have any effect (OR=1.24; 95% CI=0.52–2.94).

In a population-based case-control study among men in six Canadian provinces between 1991 and 1994, researchers reported non-statistically significantly elevated odds of multiple myeloma in relation to glyphosate use (OR=1.22; 95% CI=0.77–1.93), based upon 32 glyphosate exposed multiple myeloma case and 133 controls (Pahwa *et al.*, 2012).

Kachuri *et al.* (2013), using the same Canadian study population as above, further explored multiple myeloma in relation to days per year glyphosate used in 342 cases of multiple myeloma and 1357 controls. For ever use, the OR=1.19 and 95% CI=0.76–1.87. For light users (≤2 days/year) there was no association (OR=0.72; 95% CI=0.39–1.32; 15 exposed cases); whereas, for heavy users (>2 days/ year), there was a non-significant increased odds ratio (OR=2.04; 95% CI=0.98–4.23; 12 exposed cases). The limitation in this study was the same as the previous study (*i.e.*, the number of cases and controls exposed to glyphosate were very low).

Landgren *et al.* (2009), within the AHS study population, investigated the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS). The MGUS is considered a pre-clinical marker of multiple myeloma progression. The authors did not observe a link with glyphosate use in the AHS cohort (OR=0.50; 95% CI=0.20–1.0).

(iii) Lymphoma

The National Cancer Institute (NCI) performed a series of population-based case-control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred non-Hodgkin lymphoma (NHL) cases and controls, the identified cases were through disease registries which in many cases, were histopathologically confirmed. The investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time.

Cantor *et al.* (1992), in a case-control study of NHL interviewed a total of 622 white men and 1245 population based-controls in Iowa and Minnesota. Only 26 cases and 49 controls ever handled glyphosate yielding an OR of 1.1 with the 95% CI of 0.7–1.9. The study, however, did not adjust for exposure to other pesticides.

De Roos *et al.* (2003) used pooled analysis (n=3,417) of three case-control studies of NHL conducted in white men in Nebraska, Kansas and in Iowa and Minnesota. Based on 36 exposed cases and 61 exposed controls, the risk estimates for the association between glyphosate exposure and NHL was significant (OR=2.1; 95% CI=1.1–4.0) in the logistic regression analyses. However,

utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, there was an increase risk, but the increase was not statistically significant (OR=1.6; 95% CI=0.90–2.8). Overall, the data showed a suggestive association.

Based on the above findings, Lee *et al*., (2004) examined the relationship between asthma and pesticide exposure, and NHL. Pooling data from several midwestern states (IA, MN, and NE) increased the study sample size, and additional pesticide use information was incorporated to adjust the risk estimate (duration and frequency of use, telephone follow-up interview). The study included 872 men with NHL and 2381 frequency-matched controls. The authors reported that the OR associated with glyphosate was not statistically significantly different among those with asthma (OR=1.2; 95% CI=0.4–3.3; 6 exposed cases) and among those without asthma (OR=1.4; 95% CI=0.98–2.1; 53 exposed cases), adjusting for age, state and vital status.

The three studies discussed above (Cantor *et al*., 1992; De Roos *et al*., 2003 and Lee *et al*., 2004) reflect the same population in the AHS and used different levels of information (duration and frequency of exposure) and different analytic techniques [hierarchical regression and stratified analysis (by atopy)]. While studies with increasing levels of refinement to methodology report a stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

A population-based case–control study (Hardell and Erickson, 1999) investigated the exposure to pesticides as a risk factor for NHL in Sweden during 1987–1990. Exposure data were ascertained by comprehensive questionnaires and supplemented by telephone interviews. Of the 404 cases and 741 controls, only 4 glyphosate-exposed cases and 3 controls were included in the study. In a univariate analysis, the risk estimate was elevated, but precision was low (OR=2.3; 95% CI=0.40–13.0).

Hardell *et al*. (2002) analyzed pooled data from two case-control studies from Sweden that examined NHL (Hardell and Erickson, 1999) and another on hairy cell leukemia, a subtype of NHL (Nordstrom *et al*., 1998). In the univariate analysis glyphosate exposure was found to be significantly increased (OR=3.04; 95% CI=1.08–8.52) but, when study site, and vital status were considered in a multivariate analyses, there was a non-statistically elevated risk among glyphosate users (OR=1.85; 95% CI=0.55–6.20). However, the wide range of the CI suggest that the study is under powered and, therefore the findings do not allow definitive conclusion on the association of NHL and glyphosate exposure.

In another case-control study in Sweden (1999–2003), Eriksson *et al*. (2008) examined the effects of exposure to different agents and NHL among 910 NHL cases and 1016 non-NHL controls. Glyphosate exposure which was reported in 29 cases and 18 controls produced an OR of 2.02 (95% CI=1.10–3.71) in a univariate analysis and an OR of 1.51 (95% CI=0.77–2.94) in a multivariate analysis conducted to clarify the relative importance of exposure to different pesticides. When exposure was for more than 10 days/year, the OR was 2.36 (95% CI=1.16–4.40)

and for exposure less than 10 days/year, the OR was 1.69 (95% CI=0.7–4.07). The risk estimate was elevated also for B-cell lymphoma and glyphosate exposure (OR=1.87; 95% CI=0.998–3.51).

McDuffie *et al.* (2001) in a multicenter-population based study among men of six Canadian provinces estimated the association between glyphosate and NHL. The study included 517 cases and 1506 controls identified betwen1991and 1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of cases, implemented a two-tiered exposure questionnaire; and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the test results. There was a non-statistically significant increased risk of NHL from glyphosate exposure. The OR was 1.26 and the 95% CI was 0.87–1.80 for 51 exposed cases, adjusted for age and province and the OR was 1.20 with a 95% CI of 0.83–1.74 when adjusted for age, province and high-risk exposure (adjusted for statistically significant medical variables such as history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative).

In a follow-up study which controlled for exposure to other pesticides, the risk to NHL from glyphosate exposure was attenuated. Glyphosate exposure which was reported in 19 cases and 78 controls produced an OR of 0.92 with 95% CI of 0.54–1.55 (Hohenadel *et al.*, 2011). Within this series of studies, the authors also evaluated Hodgkin lymphoma (HL), and observed little statistical evidence of an association, using similar study design and methods. Among the 38 cases exposed to glyphosate the OR was 0.99 with a 95% CI of 0.62–1.56 (Karunanayake *et al.,* 2012).

In a hospital-based case control study conducted between 2000 and 2004 in France, authors identified 491 NHL cases and 456 age-and sex-matched controls, and performed telephone-based questionnaire to assess pesticide and other confounding variables. There was no association between NHL and glyphosate use; for the 12 exposed cases, the OR was 1.0 and the 95% CI was 0.5–2.2). For Hodgkin lymphoma, for the 6 exposed cases, the OR was 1.7 and the 95% CI was 0.6–5.0 (Orsi *et al*., 2009).

The EPILYMPH case-control study was conducted across six countries in Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain) to explore the role of occupational exposure to specific chemicals and risk of lymphoma overall, B-cell lymphoma and other subtypes. Although the study recruited 2348 cases and 2462 controls, only a very small number of cases were exposed to glyphosate (n=4) and controls (n=2). A non-significant increase in OR was observed for B-cell lymphoma (OR=3.1; 95% CI=0.6–17.1), but the estimate is unstable due to the small number of exposed cases and controls (Cocco *et al.,* 2013)

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL using data from six of the above mentioned studies (McDuffie *et al*., 2001; Hardell *et al*., 2002; DeRoos *et al*., 2003 and 2005; Eriksson *et al*., 2008; and Orsi *et al*., 2009). Since the authors identified a variety of sources of heterogeneity between publications, they calculated meta-risk ratio (RR) estimates and 95% CIs using random effect models, allowing between study heterogeneity to contribute to the variance. They reported I^2 values, which represented the

percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency. For glyphosate, the meta-risk ratio was 1.5 with a 95% CI of 1.0–2.0 and the I^2 value was 32.7% indicating greater inconsistency in these data sets. This study combined multiple smaller studies that on their own were very limited in statistical power to detect differences.

The 2015 IARC evaluation noted that fully adjusted risk estimates in two of the Swedish studies (Hardell *et al.*, 2002 and Eriksson *et al.*, 2008) were not used in the analysis conducted by Schinasi and Leon (2014). Consequently, IARC conducted a reexamination of the results of these studies. For an association between glyphosate exposure and NHL, the IARC estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65), I^2=0%; p=0.589 for heterogeneity) (IARC 2015).

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Leukemia					
Brown *et al.* (1990) Iowa and Minnesota, U.S.A.	Population-based Case-Control 1981-1984 578 cases 1245 controls	In person interview; surrogates used.	OR=0.9 (0.5-1.6) (Exposed:15 cases 49 controls)	No association between glyphosate exposure and leukemia	Vital status (alive, dead), residency (IA or MN), tobacco use, parent, sibling, or child with a lymphopoietic cancer, high risk occupation and exposure to substances (benzene, hair dyes etc) related to risk of leukemia
Nordstrom *et al.* (1998) Sweden	Population-based Case-Control 1987-1992 121 cases 484 controls	Self-reported pesticide questionnaire and follow-up telephone interview	OR=3.1 (0.8-12) (Exposed: 4 cases 5 controls)	A non-statistically significant elevated risk of hairy cell leukemia	Age, sex, country of residence (selected using matching, dissolved matching analyses) No adjustment for exposure from other pesticides
Multiple Myeloma					
Brown *et al.* (1993) Iowa, U.S.A.	Population based Case-Control 1981-1984 173cases 650 controls	Interview based questionnaire with follow-up	OR=1.7 (0.8-3.6) (Exposed: 11 cases 40 controls)	Limited power to assess association of glyphosate exposure and multiple myeloma	Age and vital status

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
De Roos *et al*. (2005) Iowa and North Carolina, U.S.A.	Prospective Cohort 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	Full data set RR =1.1 (0.5-2.4) (Exposed: 32 cases) Adjusted for age etc RR=2.6 (0.7-9.4)	No risk for full data set. Excess risk only with no missing information of 22 cases in the restricted data set (Sorahan, 2015)	Missing data on covariates when multiple adjustments were made, limiting interpretation
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=2.4 (0.8-7.3) (Exposed: 5 cases 18 controls)	No significant association with glyphosate exposure and multiple myeloma	Age, center, socioeconomic category
Pahwa *et al*. (2012) Canada	Population based Case-Control 1991-1994 342 cases 1506 controls	Self-reported pesticide use, structured interview with questionnaire; cumulative exposure (+/-10 days/yr)	OR=1.22 (0.77-1.93) (Exposed: 32 cases 133 controls)	No significant association with glyphosate exposure and multiple myeloma	Significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age group and province of residence

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Kachuri *et al.* (2013) Canadian Provinces	Population based Case-Control 1991-1994 342 cases 1357 controls	Self-administered questionnaire	For ever use OR=1.19 (0.76-1.87) Exposed: 32 cases 121controls Light (<2 d/yr) use OR=0.72 (0.39 -1.32) Exposed: 15 cases 88 controls Heavy (>2 d/yr) use OR=2.04 (0.98-4.23) Exposed: 12 cases 29 controls	No association with glyphosate exposure and multiple myeloma for ever or light users Increase for heavy users is non-significant	Relatively low response rate
Monoclonal Gammopathy of Undetermined Significance (MGUS)					
Landgren *et al.* (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 678 participants	Self-administered questionnaire	OR=0.5 (0.2-1.0)	No association with glyphosate exposure and MGUS, a premalignant disorder that often precedes multiple myeloma	Age and education

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Non-Hodgkin Lymphoma (NHL)					
Cantor *et al.* (1992) Iowa and Minnesota, U.S.A.	Population based Case-Control 1980-1983 622 cases 1245 controls	Structured interview, questionnaire response; farm activities and specific pesticide use	OR=1.1 (0.7-1.9) Exposed: 26 cases 49 controls	No association with glyphosate exposure and NHL	Vital status, age, state, smoking, family history, high risk occupation, high risk exposure. Not controlled for exposure to other pesticides.
De Roos *et al.* (2003) Iowa, Nebraska, Minnesota, Kansas, U.S.A.	Case-Control 1983-1986\Nebraska 1979-1981\Kansas 1979-1986 870 white male cases 2569 white male controls	Interview-based questionnaire, demographic	Logistic regression OR=2.1 (1.1-4.0) Exposed: 36 cases 61 controls Hierarchical regression OR=1.6; (0.9-2.8)	Significant increased OR in logistic model but in the hierarchical model, the OR attenuated and no significant association with glyphosate exposure and NHL	Age, study site, use of all other pesticides (group); hierarchal regression informed priors based on chemical-specific information
Lee *et al.* (2004a) Iowa, Nebraska, Minnesota, U.S.A	Population based Case-Control 1980-1986 872 white male cases	In person, structured interview (pesticide use, duration, frequency, first and last year used); 5-yr follow-up interview, 10-min telephone on pesticide use	Non-asthmatic OR=1.4 (0.98-2.1) (Exposed: 53 cases 91 controls) Asthmatic OR=1.2 (0.4-3.3) (Exposed: 6 cases 12 controls)	No significant association with glyphosate exposure and NHL either for asthmatics or non-asthmatics	Adjusted for age, vital status, state

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	OR=1.1 (0.7-1.9 (Exposed: 92 cases)	No significant association with glyphosate exposure and NHL	Age, smoking, other pesticides, alcohol consumption, family history of cancer, education
Hardell and Erickson (1999) Sweden	Population based Case-Control 1987-1990 404 male cases 741 male controls	Questionnaire and follow-up interview	Univariate OR=2.3 (0.4-13.0) (Exposed: 4 cases 3 controls) Multivariate OR=5.8 (0.6-54)	Some evidence of a link with glyphosate, matching variables; cannot conclude regarding causal role for any specific pesticide	Age, region, vital status (matching). Few subjects exposed. Variables used in multivariate were no specified. Study has limited power to detect an effect
Hardell *et al.* (2002) Sweden	Population based Case-Control Combined Hardell 1999 with another case-control study examining hairy cell leukemia (one of 61 types of NHL) 1987-1990 515 cases 1141 controls	Questionnaire and follow-up interview	Univariate OR=3.04 (1.08-8.52) (Exposed: 8 cases 8 controls) Multivariate OR=1.85 (0.55-6.20)	Risk attenuates when adjusted for other variables in the multivariate analysis	Age, country, study site, vital status, other pesticide exposure in the multivariate analysis

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Eriksson *et al.* (2008) Sweden	Population based Case-Control 1999-2002 910 cases 1016 controls	Questionnaire and follow-up interview	Univariate OR=2.02 (1.10-3.71) (Exposed: 29 cases 18 controls) Multivariate OR=1.55 (0.77-2.94) With <10 days/ year OR=1.69 (0.7-4.07) (Exposed: 12 cases 9 controls) With > 10 days/year OR=2.36 (1.04-5.37) (Exposed: 17 cases 9 controls) B-cell lymphoma OR=1.87 (0.998-3.51)	Suggestive association for NHL with glyphosate exposure	Age, sex, year of diagnosis. Multivariate analysis adjusted for exposure to other pesticides
McDuffie *et al.* (2001) Canada	Population based Case-Control 1991-1994 517 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	Univariate OR=1.26 (0.87-1.8) (Exposed: 51 cases 133 controls) Multivariate OR=1.20 (0.83-1.74)	No significant association with glyphosate exposure and NHL	Adjusted for statistically significantly medical variables (history of measles, mumps, cancer, allergy shots, and a positive family history of cancer) males only

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Hohenadel *et al.* (2011) Canada	Case-Control 1991-1994 513 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	OR=0.92 (0.54-1.55) (Exposed: 19 cases 78 controls)	No significant association with glyphosate exposure and NHL	Age, province and proxy respondent, males only
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.0 (0.5-2.2) (Exposed: 12 cases 24 controls)	No association with glyphosate exposure and NHL	Age, center, socioeconomic category
Cocco *et al.* (2013) Czech Republic, France, Germany, Italy, Ireland and Spain	EPICLYMPH Case-Control 1998–2003 2348 cases 2462 controls	Occupational exposure; trained interviewers conducted in person interviews with cases and controls	OR=3.1 (0.6-17.1) (Exposed: 4 cases 2 controls)	No significant association with glyphosate exposure and B-cell	Age, center, socioeconomic category
Hodgkin Lymphoma					
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.7 (0.6-5.0) (Exposed: 6 cases 15 controls)	No significant association with glyphosate exposure and HL	Age, center, socioeconomic category

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Karunanayake *et al.,* (2012). Canada	Case-Control 1991-1994 361 cases 1,506 controls	Questionnaire and follow-up interview	Univariate OR=1.14(0.74-1.76) (Exposed :38 133 controls) Multivariate OR=0.99 (0.62-1.56)	No association with glyphosate exposure and HL	History of measles, acne, hay fever, shingles and positive family history of cancer in a first-degree relative

D. Discussion

In epidemiologic studies, the quality of the exposure assessment is a major concern since the validity of the evaluations depends in large part on the ability to correctly quantify and classify an individual's exposure. During their life-time, farmers are typically exposed to multiple pesticides and several of them are used together posing a challenge for identifying specific risk factors. Moreover, there is no direct information on pesticide exposure or absorbed dose because analyses are based on self-reported pesticide use. The studies included in this epidemiology assessment relied primarily on questionnaires and interviews to describe participants' past and/or current exposure to glyphosate. Since the questionnaires are commonly used to account for exposure and capture self-reporting, it can be subject to misclassification and recall bias. For example, case-control studies are at risk of recall bias in the reporting of pesticide use in the past because cases may have spent more time thinking about past exposures than controls. This could lead to differential misclassification and bias relative risk from null. The possible effect of confounding factors, which are related to both the exposure of interest and the risk of disease, may make it difficult to interpret the results. Therefore, the ability of epidemiologic studies to provide convincing evidence of causation under such circumstances may be limited. Causation is suspected if several studies are consistent in their findings and; if the association between the agent and the risk of disease is strong (*i.e.*, high risk ratio). Support from animal data will help to make the case for causation, particularly by establishing biological plausibility and the existence of a potential mechanism. Another important consideration in assessing epidemiologic studies is that commercially formulated products (not the active ingredient) are used by farmers. For example, glyphosate is sold as Roundup®, which is a combination of the active ingredient and other chemicals that often include a surfactant (polyethyleneamine) used to enhance the spreading of spray droplets when they contact the foliage. Thus, it is possible that different glyphosate-containing formulations were used across the different studies.

Most of the studies discussed here were hypothesis-generating in nature, consisted of small sample sizes with limited power to detect associations and evaluated use of glyphosate in addition to several other pesticides and often evaluated risk of multiple different types of cancer. Therefore, the role of chance given the many different statistical tests performed and the lack of a pre-specified hypothesis, limit epidemiologic inference. This hypothesis-generating evidence observed in the studies requires further prospective follow-up studies to determine whether a true association with glyphosate is indeed null. The case-control studies are retrospective studies and are susceptible to recall bias for exposure reporting which could account for discrepancies in the study findings. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could also explain these inconsistencies in the data. In contrast, a prospective cohort study evaluates a number of diseases simultaneously and facilitates performance of periodic assessments of agricultural and other exposures. Periodic assessment of recent exposures enhances recall and reduces non-differential misclassification. The ability to determine exposure prior to the onset of a disease eliminates the case-recall bias, which was an issue identified as a weakness in case-control studies.

IV. EVALUATION OF CARCINOGENICITY IN ANIMALS

A total of 11 chronic toxicity/carcinogenicity studies (7 rat and 4 mouse) were included in this weight of evidence review. Of these, six studies were submitted for review to EPA under the registration/reregistration programs including two studies in rats (MRID No. 496311701 and 49704601) and one in mouse (MRID No. 49631702) not previously reviewed. Data for review of the other five studies were obtained from a published review article by Greim *et al.*, 2015 and were available online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423. The IARC acknowledged the Greim *et al.,* (2015) review article, but did not evaluate the studies cited in the review because the information provided in the review and its supplement was insufficient.

For this assessment, each study reported in the Greim *et al.,* (2015) review article was evaluated in accordance with the agency's 2012 Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf). In accordance with this guidance, the following four studies were not included in this weight of evidence assessment since there is low confidence were determined to be unreliable for carcinogenicity evaluation.

- A two year feeding study in Sprague-Dawley rats (Excel, 1997) was not included due to the lack of test article characterization (no purity of test material).

- The two-year drinking water study in Wistar rats reported by Chruscielska *et al.*, (2000) was not included since the tested material was a formulated product (13.6% ammonium salt) and there were a number of deficiencies (lack of purity, water consumption and body weight data) in the conduct and reporting of the study.

- An initiation-promotion study (George *et al.*, 2010) in male Swiss mice that tested a commercial formulation of glyphosate (41%) with study deficiencies (*e.g.* small number (20) of animals, tested only males, and lack of histopathological examination).

- A carcinogenicity study in Swiss mice (Feinchemie Schwebda, 2001) was not included due to the presence of viral infection within the colony, which confounded the interpretation of the study findings. Malignant lymphomas were reported in this study in all groups. However, lymphomas are one of the most common types of spontaneous neoplastic lesions in aging mice (Brayton *et al.*, 2012). Murine leukemia viruses (MuLVs) are a common cause of lymphoma in many different strains of mice (Ward 2006). Tadesse-Heath *et al.* (2000) reported 50% lymphoma (mostly B-cell origin) incidence in a colony of Swiss mice. Although the incidences in this study were within or near the normal variation of background occurrence, it is not clear whether or not the viral component may have contributed to incidence value reported or the lower survival seen at the high dose in the study. Raw data are not available to perform appropriate statistical analyses of the lymphomas correcting for the intercurrent mortality.

A. Carcinogenicity Studies in Rats

1. Lankas, G, P. A Lifetime Study of Glyphosate in Rats. December 23, 1981. Unpublished report No. 77-2062 prepared by Bio Dynamics, Inc. EPA Accession. No. 247617 – 247621. MRID No. 00093879.

a. Experimental Design

Groups of Sprague-Dawley rats (50/sex/dose) were fed diets containing glyphosate (98.7%, pure) at concentrations of 0, 30, 100 or 300 ppm for 26 months. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in females were maintained.

b. Survival Analysis

There were no treatment-related effects on survival at any dose level.

c. Discussion of Tumor Data

There was an increase in the incidences of interstitial cell tumors in the testes of male rats at the low (3/5; 6%), mid (1/50; 2%) and the high dose (6/50; 12%; P=0.013 pairwise comparison) when compared to controls (0/50; 0%). In 1991, HED's Cancer Peer Review Committee (CPRC) did not consider the increases to be treatment-related based on the following weight of evidence considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5%; range, 3.4% to 6.7%) and 5) no interstitial cell tumors were seen when tested at much higher doses in the same strain of rats in an another study (discussed below). The CARC agreed with the CPRC conclusion and rationale and noted additional rat studies which also showed no effect on interstitial cell tumors.

Although there was no evidence of a treatment-related increase in the incidences of pancreatic islet cell tumors in male rats, the data are presented in Table 4 since this tumor also seen in the second study discussed below.

Table 4. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats (MRID 00093879)				
Tumor Type	0 ppm	30 ppm	100 ppm	300 ppm
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Combined (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

d. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

The CPRC concluded that the highest dose tested was not adequate to assess the carcinogenic potential of glyphosate. Consequently, a second study was conducted (discussed below).

2. Stout, L. D. and Rueckerf, P.A. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; September, 26, 1990, MRID No. 41643801; Historical Controls; MRID No. 41728701.

a. Experimental Design

Groups of Sprague-Dawley rats (60/sex/dose) were fed diets containing glyphosate (96.5%, pure) at dietary concentrations of 0, 2000, 8000 or 20,000 ppm 24 months. These levels were equivalent to 0, 89, 362 or 940 mg/kg/day, respectively, for the males and 0, 113, 457 or 1183 mg/kg/day, respectively, for the females. An interim sacrifice was conducted on 10 rats/sex/dose at 12 months.

b. Discussion of Tumor Data

The most frequently seen tumors were pancreatic cell adenomas, hepatocellular adenomas and thyroid C-cell adenomas in males. Data for these tumors and the respective historical control data are presented in Tables 5 thru 11.

Pancreatic cell adenomas are presented in Table 5 and the historical control data are presented in Table 6. Hepatocellular adenomas seen in males are presented in Table 7 and the historical control data are presented in Table 8. The thyroid C-cell adenomas and/or carcinomas observed in males and females are presented in Tables 9 and 10, respectively, and the historical control data are presented in Table 11.

(i) Pancreas

There was no statistically significant trend test by dose for pancreatic islet cell tumors. Increased incidences of adenomas only were observed at the low- and high-dose groups but not at the mid-dose group.

Table 5. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas	1/43[a]	8/45	5/49	7/48[b]
(%)	(2)	(18)	(10)	(15)
P =	0.170	0.018*	0.135	0.042*
Carcinomas	1/43[c]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
P=	0.159	0.409	0.467	0.472
Combined	2/43	8/45	5/49	7/48
(%)	(2)	(18)	(10)	(15)
P=	0.241	0.052	0.275	0.108

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 81 in the 20,000 ppm group
c. First carcinoma observed at week 105 in the controls (0 ppm)
* Significant in a pair-wise comparison (P<0.05)

Historical control data on the incidence of pancreatic islet cell adenomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 6.

Table 6. Historical Control Data — Pancreatic Islet Cell Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)

Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Tumor Incidence	2/68	5/59	4/69	1/57	5/60	3/60	3/59
%	2.9%	8.5%	5.8%	1.8%	8.3%	5.0%	5.1%

The CPRC concluded that the pancreatic islet cell adenomas are not treatment-related based on the following weight of evidence considerations: 1) although the incidences at the low (18%) and high (15%) dose groups exceeded the historical control range (1.8–8.5%), there was lack of statistical significance in Cochran-Armitage trend test; 2) the tumor incidence in the concurrent control was at the low end of the historical control range; 3) considerable inter-group variability in the numbers of males with tumors (*i.e.*, no dose-response); 4) there were no preneoplastic changes; 5) there was no progression from adenomas to carcinomas; and 6) the apparent statistical significance of the pairwise comparisons of the treated groups with the concurrent control may be due to the low incidences in the controls and not to an actual carcinogenic response. Furthermore, the incidences of pancreatic cell tumors for the two studies did not show dose-response and the incidences were within the historical control range (0 to 17%) reported in the open literature (Arnold *et al.,* 1985; Borelli *et al.*, 1990; Borzelleca *et al.*, 1986, 1989, 1990; Burnett *et al.*, 1988; Trochimowicz *et al.*, 1988). The CARC agreed with the CPRC conclusion and rationale and noted subsequent rat studies which also showed no effect on islet cell tumors.

(ii) Liver

There was a dose trend for adenomas only. There were no statistically significant increases in the occurrence of benign or malignant hepatocellular tumor types (Table 7). The observed variations in incidence were within the range of the historical control data.

Table 7. Glyphosate: Hepatocellular Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/44[a] (5) 0.016*	2/45 (4) 0.683	3/49 (6) 0.551	7/48[b] (15) 0.101
Carcinomas (%) P =	3/44 (7) 0.324	2/45 (4) 0.489	1/49 (2) 0.269	2/48[c] (4) 0.458
Adenoma/Carcinoma (%) P =	5/44 (11) 0.073	4/45 (9) 0.486	4/49 (8) 0.431	9/48 (19) 0.245

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 88 in the 20000 ppm group
c. First carcinoma observed at week 85 in the 20000 ppm group

Historical control data on the incidence of hepatocellular adenomas and carcinomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 8.

Table 8. Historical Control Data : Hepatocellular Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)							
Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Adenomas	5/60 (8.3%)	11/68 16.2%)	1/70 (1.4%)	3/59 (5.1%)	11/60 (18.3%)	5/60 8.3%)	4/60 (6.7%)
Carcinomas	4/60 (6.7%)	0/68 (0%)	1/70 (1.4%)	2/59 (3.4%)	3/60 (5%)	1/60 (1.7%)	0/60 (0%)

The CPRC concluded that the slightly increased incidence of adenomas in male rats are not treatment-related since: 1) the increase was not statistically significant in pairwise comparison with the controls; 2) the incidences were within the historical control range; 3) except for a single animal at the mid-dose late in the study (89 weeks), no hyperplasia, preneoplastic foci or other non-neoplastic lesions were seen; and 4) there was no evidence of progression from adenomas to carcinomas. The CARC agreed with the CPRC conclusion and rationale.

(iii) Thyroid

The increased incidences in C-cell adenomas observed at the mid and high-dose groups of rats of both sexes did not show a statistically significant difference in pairwise comparisons with the controls (Table 9 and 10, respectively). There was a dose trend observed for adenomas and adenomas/carcinomas in females (P=0.03). Historical control data are presented in Table 11.

Table 9. Glyphosate: Thyroid C-Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/54[a, b] (4) 0.069	4/55 (7) 0.348	8/58 (14) 0.060	7/58 (12) 0.099
Carcinomas (%) p =	0/54 (0) 0.452	2/55[c] (4) 0.252	0/58 (0) 1.000	1/58 (4) 0.518
Adenoma/Carcinoma (%) p =	2/54 (11) 0.077	6/55 (11) 0.141	8/58 (14) 0.060	8/58 (14) 0.060

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 54 in the controls
c. First carcinoma observed at week 93 in the 20,000 ppm

Table 10. Glyphosate: Thyroid C-Cell Tumors in Female Sprague Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P=	2/57[a] (4) 0.031*	2/60 (7) 0.671	6/59[b] (10) 0.147	6/55 (11) 0.124
Carcinomas (%) P=	0/57 (0) 0.445	0/60 (0) 1.000	1/59[c] (2) 0.509	0/55 (0) 1.000
Adenoma/Carcinoma (%) p=	2/57 (4) 0.033*	2/60 (3) 0.671	7/59 (12) 0.090	6/55 (11) 0.124

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 72 in the controls
c. First carcinoma observed at week 93 in the 8000 ppm group.

Table 11. Historical Control Data – Thyroid C-cell Tumors in Sprague-Dawley Rats (MRID No. 41728701)		
Tumor Type	Males	Females
Adenomas	1.8 – 10.6%	3.3 – 10.0%
Carcinomas	0.0 – 5.2%	0.0 – 2.9%

The CPRC concluded that the thyroid tumors in either sex are not treatment-related since: 1) the increased incidences exhibited no statistically significant trend or pairwise comparisons with the controls in males; 2) in females, there was a trend but no pairwise significance; 3) there was no progression from adenomas to carcinomas; and 4) there was no dose-related increase in severity of grade or incidence of hyperplasia in males or females. The CARC agreed with the CPRC conclusion and rationale and noted other rat studies which showed no effect on thyroid C-cell tumors.

c. Non-Neoplastic Lesions

There were no treatment-related precursor lesions at any dose level.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was near or beyond the limit dose (1000 mg/kg/day).

3. **Atkinson, C., Strutt, A., Henderson, W., et al. (1993). 104-Week chronic feeding/ oncogenicity study in rats with 52-week interim kill. Inveresk Research International (IRI), Tranent, Scotland. Study No. 438623; IRI Report No. 7867. April 7, 1993. MRID No. 49631701. Unpublished.**

a. Experimental Design

In a combined chronic toxicity/carcinogenicity study, glyphosate (98.9% pure) was administered to 50 male and female Sprague-Dawley rats/sex/dose in the diet at 0, 10, 100, 300, and 1000 mg/kg/day for 104 weeks. An interim sacrifice was conducted on 15 rats/sex/dose after 52 weeks of treatment.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

There were no treatment-related increases in the occurrence of any tumor type in this study.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was the limit dose (1000 mg/kg/day) and at this dose increased salivary gland weight accompanied by cellular alterations in the mandibular and/or parotid glands occurred in both males and females.

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4. **Brammer. (2001). Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Rats. Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK: Syngenta. (MRID No. 49704601).**

a. Experimental Design

In a combined chronic toxicity study, glyphosate acid (97.6% pure) was administered to groups of Wistar rats in the diet. Groups of 52 male and 52 female rats received diets containing 0, 2,000, 6,000, and 20,000 ppm glyphosate for 24 months. The achieved doses were 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437 or 1498 mg/kg/day in females, respectively. Three satellite groups of 12 rats/sex/group were also included for

interim sacrifice at 12 months of treatment. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

As shown in Table 12, there was an increase in the incidence of hepatocellular adenomas in male rats at the high dose when compared to controls. This increase was not considered to be treatment-related due to 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the range (0–11.5%) of historical controls for this strain (Wistar) of rats in 26 studies conducted during the relevant time period (1984–2003) at the testing laboratory; and 5) the 0% incidence in concurrent controls is lower than the average background incidence for liver adenomas in male Wistar rats.

Table 12. Liver Adenomas in Male Wistar Rats Fisher's Exact Test and Exact Trend Test Results

	0	2000	6000	20000
Adenomas	0/52[a]	2/52	0/52	5/52
(%)	(0)	(4)	(0)	(10)
P =	0.00804**	0.24757	1.00000	0.02826*

a =Number of tumor-bearing animals/Number of animals examined.

In addition, statistically higher survival (P=0.02) was observed in males at 20,000 ppm at the end of 104 weeks relative to controls, and an overall trend for improved survival was observed in treated males (P=0.03). The inter-current (early) deaths were 37/52, 36/52, 35/52, and 26/52 for the control, low, mid and high dose groups, respectively. The terminal deaths were 16/52, 17/52, 18/52, and 26/52 for the control, low, mid and high dose groups, respectively. This survival bias in the high dose group could easily explain a modestly higher incidence of an age-related background tumor like liver adenoma (and fits with lack of associated lesions). In the 1990 study in Sprague-Dawley rats (MRID No. 41643801) there was also a weak but significant trend test for liver adenomas in males (P=0.02, no pairwise); however, in that study adenomas in all treatment groups were still within the historical control and the CPRC concluded that this effect was not treatment-related, as discussed above. The lack of increased liver tumor incidence in the other rat studies provide additional evidence for lack of an actual carcinogenic response in the liver.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in any organs of either sex at any dose level tested.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes (1214 mg/kg/day in males and 1498 mg/kg/day in females) exceeded the limit dose (1000 mg/kg/day). Treatment-related findings at these doses were observed in the liver and kidney, notably renal papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, hematuria and slight increases in the incidence of proliferative cholangitis and hepatitis.

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5. Feinchemie Schwebda. (1996). Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats. Bangalore, India: Rallis India, Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (96.0-96.8% pure) was administered to groups of Wistar rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 100, 1000, and 10000 ppm glyphosate for 24 months. The average achieved doses were 0, 7.4, 73.9, and 740.6 mg/kg/day. Parameters evaluated included clinical signs, body weights, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy, and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no non-neoplastic lesions at any dose level in either sex.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The doses tested were determined to be adequate in both sexes since the highest dose tested (741 mg/kg/day) approached the limit dose (1000 mg/kg/day).

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6. Arysta Life Sciences. (1997a). HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (94.6–97.6% pure) was administered to groups of Sprague-Dawley rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 3000, 10000, or 30000 ppm glyphosate for 24 months. The achieved doses were 0, 104, 354 or 1127 mg/kg/day in males and 0, 115, 393, or 1247 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose 10,000 ppm (1127 mg/kg/day in males and 1247 mg/kg/day in females) exceed the limit dose (1000 mg/kg/day) and there were increased cecum weights, distension of the cecum, loose stool, follicular hyperkeratosis and/or folliculitis/follicular abscess of the skin, and decreased body weights.

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7. **Nufarm. (2009a). Glyphosate Technical: Dietary Combined Chronic Toxicity/ Carcinogenicity in the Rat. Shardlow, Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015)**.

a. Experimental Design

In a combined chronic toxicity study, glyphosate (95.7% pure) was administered to groups of Wistar rats in the diet. Groups of 51 rats/sex/group received diets containing 0, 1500, 5000, and 15,000 ppm glyphosate for 24 months. To ensure that a received limit dose of 1000 mg/kg/day was achieved, the highest dose level was progressively increased to 24000 ppm. The achieved doses were 0, 86, 285 or 1077 mg/kg/day in males and 0, 105, 349 or 1382 mg/kg/day, in females. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in either sex at any dose level.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest doses 1077 mg/kg/day in males and 1382 mg/kg/day in females exceed the limit dose (1000 mg/kg/day).

B. Carcinogenicity Studies in Mice

1. Knezevich, A.L and Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamic Inc., dated July 21, 1983. Report No. 77-2011. EPA Accession No. 251007 – 251009, and 251014.

a. Experimental Design

In a carcinogenicity study, groups of 50 male and female CD-1 mice received glyphosate (99.78%, pure) at dietary levels of 0, 1000, 5000, or 30,000 ppm for two years. These doses were equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, and histopathological examination.

b. Discussion of Tumor Data

The incidences of renal tubule adenomas were as follows: 0/49 in the controls; 0/49 at the low-dose; 1/50 at the mid-dose; and 3/50 at the high dose (TXR No. 0004370).

In 1985, the Registrant directed a re-evaluation of the original renal section by a consulting pathologist (Dr. Marvin Kuschner). This evaluation identified a small renal tubule adenoma in one control male mouse (animal number 1028) which was not diagnosed as such in the original pathology report (TXR No. 0004855).

In 1986, at the request of the agency, additional renal sections (3 sections/kidney/mouse spaced at 150 micron intervals) were evaluated in all control and all glyphosate-treated male mice in order to determine if additional tumors were present. The additional pathological and statistical evaluations concluded that the renal tumors in male mice were not compound-related (TXR No. 0005590).

At the request of the agency, the Pathology Work Group (PWG) examined all sections of the kidneys including the additional renal sections. The renal tubular-cell lesions diagnosed by the PWG are presented below in Table 13. The PWG noted that because differentiation between tubular-cell adenoma and tubular-cell carcinoma is not always clearly apparent and because both lesions are derived from the same cell type, it appropriate to combine the incidences for purposes of evaluation of statistical analysis. Statistical analyses are presented in Table 14. The PWG unanimously concluded that these lesions are not compound-related based on the following considerations: 1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the controls and there was no evidence of a significant linear trend; 3) multiple renal tumors were not found in any animal; and 4) compound-related nephrotoxic lesions,

including pre-neoplastic changes, were not present in male mice in this study (TXR No. 0005590).

Table 13. Glyphosate: Kidney Tumor in Male CD-1 Mice — PWG				
Dose/Tumor Type	Control	1000 ppm	5000 ppm	30,000 ppm
	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Tubular-cell adenoma	1/49	0/50	0/50	1/50
Tubular-cell carcinoma	0	0/50	1/50	2/50
Combined incidence	1/49 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)

Statistical analysis of the male mouse renal tumors diagnosed by the PWG are presented below in Table 14.

Table 14. Kidney Tumors in Male CD-1 Mice — PWG Cochran-Armitage Trend & Fisher's Exact Test (MRID 00130406)				
Tumor Type	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Adenomas (%) P =	1/49 (2) 0.4422	0/49 (0) 1.0000	0/50 (0) 1.00000	1/45 (2) 0.7576
Carcinomas (%) P =	0/49 (0) 0.0635	0/49 (0) 1.0000	1/50 (2) 0.5051	2/50 (4) 0.2525
Combined (%) P =	1/49 (2) 0.0648	0/49 (0) 1.0000	1/50 (2) 0.7576	3/50 (6) 0.3163

Historical control data from the testing laboratory (Bio-dynamics) during the glyphosate-study period (1976-1982) are presented in Table 15.

Table 15. Historical Control Data- Kidney tumors in CD-1 Mice — Bi/dynamics Inc.														
Study I.D	A		B		C		D		E		F		G	
Study Period	6/78 - 7/80		12/77- 4/80		12/77- 3/80		10/78- 4/81		11/78- 4/81		11/77- 4/80		10/77-4/80	
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
Tubular Adenoma		1	0	0	0	0	0	0	0	2	0	0	0	0

Historical control data from 14 studies conducted between 1977 and 1981 at the testing laboratory indicated that the mouse renal tumors ranged from 0 to 3.3% and the incidence in the current study (3/50; 6%) exceeded the upper limit of the historical control range (TXR No. 0007252).

The CPRC determined that glyphosate produced an equivocal carcinogenic response in male mice characterized by an increased incidence of renal tubular neoplasms. The biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls for adenomas, carcinomas and the combined tumors; b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (*e.g.* tubular necrosis/regeneration, hyperplasia, hypertrophy, etc.), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males; e) although the incidences exceeded the historical control, this finding did not override the lack of statistical significance of comparison to the concurrent controls. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not consider the renal tumors to be treatment-related. The CARC reaffirmed the CPRC conclusion and rationale. Also, the lack of increased renal tumors in the other mouse studies in the same strain provides additional evidence for lack of an actual carcinogenic response in the kidneys.

c. Non-Neoplastic Lesions

The incidence of centrilobular hepatocyte hypertrophy was slightly but not significantly increased in high-dose male mice at terminal sacrifice if all mice were included in the analyses. Centrilobular hepatocyte necrosis was significantly ($P \leq 0.01$) increased in high-dose male mice (10/50; 20%) compared to controls (2/49; 4%). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice. There was a dose-dependent increase in the proximal tubular epithelial basophilia in female mice; the incidences were: 0/50 (0%) in the controls, 2/50 (4%) at the low dose, 4/50 (8%) at the mid dose, and 9/50 (18%) at the high dose ($P \leq 0.01$). All other tissue alterations occurred sporadically and were found with approximately equal frequency and severity in control and treated animals. These were considered unrelated to glyphosate treatment.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The high dose tested in males (4945 mg/kg/day) and females (6069 mg/kg/day) was approximately 4 to 6-fold higher than the limit dose (1000 mg/kg/day), which produced highly significant reduction in body weights in both sexes. Therefore, the doses tested were determined to be adequate to assess the carcinogenic potential of glyphosate in this study.

2. Atkinson, C., Martin, T., Hudson, P., and Robb, D. (1993). Glyphosate: 104 week dietary carcinogenicity study in mice. Inveresk Research International, Tranent, EH33 2NE, Scotland. IRI Project No. 438618. April 7, 1993. MRID 49631702.

a. Experimental Design

In a carcinogenicity study, glyphosate (97.5 – 100.2% pure) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. No interim sacrifices were performed. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, necropsy and histopathological examination.

b. Discussion of Tumor Data

As shown in Table 16, hemangiosarcomas were found in 4/45 (9%) high-dose male mice compared to none in the controls. In the treated mice at the high dose, one had the tumors present in the liver and spleen, one had the tumor present in the liver only, one had the tumors present in the liver, spleen, and prostate, and one had the tumor present in the spleen only. No hemangiosarcomas were found in the control or low- and mid-dose mice.

Table 16. Hemangiosarcomas in Male CD-1 Mice Fisher's Exact Test and Exact Trend Test Results

Dose (mg/kg/day)	0	100	300	1000
Hemangiosarcomas	0/47[a]	0/46	0/50	4/45
(%)	(0)	(0)	(0)	(9)
P =	0.00296**	1.00000	1.00000	0.05332

a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in hemangiosarcomas in male mice was not considered to be treatment-related due to 1) tumors seen only at the limit dose; 2) absence of statistical significance in the pairwise analysis; 3) the incidences was near or the same as the upper limit (0–8%) for the performing laboratory; 4) hemangiosarcomas were not seen in male mice in the other three studies when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4348–5874 mg/kg/day) in this strain of mouse; 6) the considerable inter-group variability in the number of female mice with this tumor (0, 2 , 0 and 1 in the control, low-, mid- and high-dose groups, respectively); 7) Hemangiosarcomas are commonly observed in mice as both spontaneous and treatment-related tumors arising from endothelial cells; 8) hemangiosarcomas appear in both sexes but are generally more common in males (CD-1); 9) As vascular tumors, they can occur at different sites but liver and spleen tend to be the most common sites in male mice.

c. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose tested was the limit dose (1000 mg/kg/day).

3. **Arysta Life Sciences. (1997b). HR-001: 18-Month Oncogenicity Study in Mice. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015)**.

a. Experimental Design

In a carcinogenicity study, groups of ICR-CD-1 mice (50/sex/group received diets containing glyphosate (94.6–97.6% pure) at 0, 1600, 8000 or 40,000 ppm for 18 months. The achieved doses were 0, 165, 838 or 4348 mg/kg/day in males and 0, 153, 787 or 4116 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes exceeded (4-fold) the limit dose (1000 mg/kg/day).

4. Nufarm. (2009b). Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In another feeding study, CD-1 mice (50/sex/dose) received glyphosate (94.6–97.6%, pure) at 0, 500, 1500, or 5000 ppm for 18 months. The calculated test substance intake was 0, 85, 267 or 946 mg/kg/day. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, gross necropsy and histopathological examination.

b. Discussion of Tumor Data

In male mice at the high dose (5000 ppm) there were increases in the incidences of adenocarcinomas of the lung and malignant lymphomas as shown in Tables 17. For the lung adenocarcinomas, the increases did not reach statistically significant pairwise differences, although the trend was significant. For the malignant lymphomas there was a trend and pairwise significance. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

Table 17. Lung Adenocarcinomas and Malignant Lymphomas in Male CD-1 Mice (Greim *et al.*, 2015)
Fisher's Exact Test and Exact Trend Test Results

Dose (ppm)	0	500	1500	5000
Lung Adenocarcinoma	5/51[a]	5/51	7/51	11/51
(%)	(10)	(10)	(14)	(22)
P =	0.02906**	0.62953	0.37996	0.08609
Malignant Lymphoma	0/51	1/51	2/51	5/51
(%)	(0)	(2)	(4)	(10)
P =	0.006633**	0.50000	0.24752	0.02820*

a= Number of tumor bearing animals/Number of animals examined.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in lung adenocarcinomas was not considered to be treatment-related due to: 1) absence of statistical significance in the pairwise analysis; 2) the incidences in all treatment groups including the controls were within the historical control range (1.43–26%) for the performing laboratory; and 3) lung tumors were not seen in the other three studies when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

Historical control data and results from the 5 studies can be used to put this finding into perspective. The malignant lymphomas were not considered to be treatment-related since the 0% incidence of this lesion in the concurrent control for male mice was lower than the historical control mean (4.5%) and range (1.5–21.7%) in this strain and age of mice (Gikins and Clifford, 2005; Son and Gopinath, 2004). Therefore, the apparent statistical significance of the pairwise comparisons of the high dose male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response. In addition, malignant lymphomas were not seen in the other three studies in this strain of mice when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

c. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose (947 mg/kg/day) tested approached the limit dose (1000 mg/kg/day).

IV. TOXICOLOGY

A. Metabolism

Single or repeated doses of radiolabeled ^{14}C-glyphosate were administered orally to male and female Sprague-Dawley rats. Following a single oral dose of, ^{14}C-glyphosate, 30 to 36% of the dose was absorbed and less than 0.27% of the dose was eliminated as CO_2. 97.5% of the administered dose was excreted in the urine and feces as the parent compound, glyphosate. Amino methyl phosphonic acid (AMPA) was the only metabolite found in urine (0.2–0.3% of the administered dose) and feces (0.2–0.4% of the administered dose). Less than 1.0% of the absorbed dose remained in tissues and organs, primarily in bone tissue. Repeated dosing at 10 mg/kg did not significantly change the metabolism, distribution or excretion of glyphosate.

In a second study, male and female Sprague-Dawley rats received single intraperitoneal injections of radiolabeled ^{14}C-glyphosate at 1150 mg/kg. Blood samples were collected 0.25, 0.50, 1, 2, 4, 6 and 10 hours after injection. Femoral bone marrow samples were collected from one third of the male and female rats sacrificed at 0.5, 4, or 10 hours after injection. Thirty minutes after injection of glyphosate, the concentration of radioactivity in the bone marrow of male and female rats was equivalent to 0.0044% and 0.0072%, respectively, of the administered dose. Assuming first order kinetics, the decrease in radioactivity in bone marrow occurred with a half-life of 7.6 and 4.2 hours for males and females, respectively. Similarly, the half-lives of the radioactivity in plasma were approximately 1 hour for both sexes. These findings indicate that very little glyphosate reaches bone marrow, that it is rapidly eliminated from bone marrow, and that it is even more rapidly eliminated from plasma.

B. Mutagenicity

In 1991, the Carcinogenicity Peer Review Committee concluded that there was no evidence of genotoxicity for glyphosate based on negative findings in submitted guideline studies for the bacterial reverse mutation test (MRID 00078620), *in vitro* mammalian cell gene mutation test in CHO cells (MRID 00132681), *in vivo* mammalian bone marrow chromosomal aberration test (MRID 00132683) and a "rec assay" used to detect DNA-damaging agents in *Bacillus subtilis* (MRID 00078619) (TXR 0008898).

Glyphosate has also been evaluated for its genotoxic potential in other regulatory and published literature studies. Extensive reviews of the available genotoxicity studies for glyphosate and glyphosate products were conducted by Williams *et al.* (2000) and by Kier and Kirkland (2013). IARC also conducted a review of the publically available genetic toxicity data for glyphosate and glyphosate-based formulations (IARC, 2015).

Williams *et al.*, (2000) concluded that "glyphosate is neither mutagenic nor clastogenic." Similarly, Kier and Kirkland (2013) concluded a "lack of genotoxic potential for both glyphosate and glyphosate based formulations (GBFs) in core gene mutation and chromosomal effect endpoints." Kier and Kirkland (2013) also stated that "the observations of DNA-damage effects seems likely to be secondary to cytotoxic effects." However, IARC (2015) concluded that "there is strong evidence that glyphosate causes genotoxicity." It should be noted that the IARC's conclusion was based not only on studies conducted with the active ingredient but also on studies conducted with the formulation products such as Roundup. Roundup is a combination of the active ingredient and other chemicals, including a surfactant (polyoxyethyleneamine) which enhances the spreading of spray droplets when contact foliage. Of note, the review article by Kier and Kirkland (2013) and supplemental information provided on the publisher's website were not considered in the IARC evaluation.

In this assessment, the CARC considered a total of 54 studies including those submitted to the agency under 40 CFR Part 158 as well as the studies presented in the review articles by Williams *et al.* (2000), Kier and Kirkland (2013), and the IARC monograph (2015). Consistent with OPP's Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf), literature studies discussed in the reviews such as IARC that did not meet the Klimisch criteria for reliability (*e.g.* lack of adequate glyphosate purity information for the test material) were not considered by the CARC. The CARC determined the mutagenic potential of glyphosate in humans by conducting a weight-of-evidence evaluation of the results from the cited bacterial reversion (Ames) assays, *in vitro* mammalian gene mutation assays, *in vitro* and *in vivo* chromosomal aberration and micronucleus assays as well as other relevant assays evaluating DNA damage.

1. Bacterial reverse mutation assays

As shown in Table 18, glyphosate was not mutagenic in any of the *in vitro* bacterial mutation assays using *S. typhimurium* or *E. coli* tester strains with or without microsomal S9 metabolic activation. These results are consistent with the negative findings in the previously reviewed EPA guideline (870.5100) bacterial reverse gene mutation study (MRID 00078620).

Table 18. Results from Bacterial Reverse Gene Mutation Assays[1]

Author	Cell/Strain[2]	Purity	Highest test concentration	Results –S9	Results +S9
Akanuma,M. (1995)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.7%[3]	5000 µg/plate	Negative	Negative
Callander, R.D. (1996)	TA98, TA100, TA1535, TA1537; WP2P and WP2*uvr*A	95.6%[3]	5000 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	76.1%[4]	100 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	96.4%	3160 µg/plate	Negative	Negative
Flügge, C. (2009)	TA98, TA100, TA102, TA1535, TA1537	98.8%	3160 µg/plate	Negative	Negative
Jensen, J.C. (1991)	TA98, TA100, TA1535, TA1537	98.6%	2500 µg /plate w/o S9; 5000 µg /plate w/ S9	Negative	Negative
Li and Long (1988)	TA98, TA100, TA1535, TA1537, TA1538;	98%	5000 µg/plate	Negative	Negative
NTP (1992)	TA97, TA100, TA1535	98%	10,000 µg /plate	Negative	Negative
Schreib, G. (2010)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96%	5000 µg/plate	Negative	Negative
Shirasu et al. (1978)	TA98, TA100, TA1535, TA1537, TA1538 and WP2*uvr*A	98.4%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007c)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.0%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007a)	TA98, TA100, TA1535, TA1537; WP2uvrA	95.1%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009b)	TA98, TA100, TA1535, TA1537;WP2P and WP2*uvr*A	96.3%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009a)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96.66%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007b)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	97.7%	5000 µg/plate	Negative	Negative
Suresh, T.P. (1993)	TA98, TA100, TA1535, TA1537, TA1538	96.0%	1000 µg/plate	Negative	Negative
Thompson, P.W. (1996)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.3%	5000 µg/plate	Negative	Negative

1. Studies cited in Williams *et al*. (2000), Kier and Kirkland (2013), or IARC monograph.
2. *S. typhimurium* strains (TA97, TA98, TA100, TA102, TA1535, TA1537, and/or TA1538) or *E. coli* strains (WP2P and WP2*uvr*A)
3. Glyphosate acid
4. Monoammonium glyphosate salt

2. *In vitro* mammalian cell gene mutation assays

Glyphosate did not induce forward mutations in mouse lymphomas cells or Chinese hamster ovary (CHO) cells in the presence or absence of metabolic (S9) activation (Table 19).

Table 19. Results from mammalian gene mutation assays[1].

Author	Assay Type	Cell type	Purity	Highest conc.	Result -S9	Result +S9
Clay (1996)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	95.6%	1.0 mg/mL	Negative	Negative
Jensen, J.C. (1991)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	98.6%	5.0 mg/mL	Negative	Negative
Li and Long (1988)	*In vitro* mammalian gene mutation	CHO cells/ HGPRT locus	98%	22.5 mg/mL	Negative	Negative

1. Studies cited in Williams's *et al.* (2000), Kier and Kirkland (2013), or IARC monograph.

3. *In vitro* chromosomal aberration assays

Lioi *et al.* (1998a, 1998b) reported positive findings for chromosomal aberrations in human and bovine lymphocytes treated with glyphosate *in vitro* in the absence of S9 activity. As discussed in the Williams review, there is less confidence in the Lioi *et al.* results based on the use of an unusual 72-hour treatment protocol and the observation of reduced cell growth in glyphosate-exposed cells (an indication of a toxic effect) which can affect the evaluation of the study. Lioi *et al.* also reported chromosomal damage in lymphocytes treated with other known non-genotoxic pesticides in this study at concentration ranges similar to where they reported effects for glyphosate. By contrast, when the tests were performed according to the OECD guideline, Van de Waart (1995) reported no significant increase in chromosomal aberrations in human lymphocytes treated with up to 0.56 mg/mL (-S9) and 0.33 mg/mL (+S9) glyphosate, which are concentrations 3 orders of magnitude higher than those at which Lioi *et al.* reported aberrations. Glyphosate was negative in two other *in vitro* chromosomal aberrations studies using human lymphocytes (Fox, 1998; Manas *et al.* 2009) and did not induce chromosomal aberrations in Chinese hamster lung cells (Matsumoto, 1995; Wright, 1996). A summary of the findings is presented in Table 20.

Table 20. Results from *in vitro* chromosomal aberration assays[1].

Authors	Assay	Cell type	Purity	Highest test concentration	Result -S9	Result +S9
Van de Waart (1995)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	0.56 mg/mL with S9; 0.33 mg/mL w/o S9	Negative	Negative
Fox, V. (1998)	Chromosome Aberration	Human peripheral lymphocytes	95.6%[2]	1250 ug/mL	Negative	Negative
Lioi et al. (1998a)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	1.4 mg/L	Positive	Not Tested
Manas et al. (2009)	Chromosomal Aberration	Human peripheral lymphocytes	96%	6 mM	Negative	Not Tested
Lioi et al. (1998b)	Chromosomal Aberration	Bovine peripheral lymphocytes	>98%	2.9 mg/L	Positive	Not Tested
Matsumoto, K. (1995)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.68%[2]	1000 ug/mL	Negative	Negative
Wright, N.P. (1996)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.3%	1250 ug/mL	Negative	Negative

1. Studies cited in Williams *et al*., (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

4. *In vivo* micronucleus and chromosomal aberration assays

Numerous studies were evaluated to determine the potential for glyphosate to induce micronuclei in rodent bone marrow cells. Studies included both intraperitoneal (IP) and oral routes of glyphosate administration. In a literature study by Bolognesi *et al.* (1997), the authors reported an induction of micronuclei in male mice treated with up to 300 mg/kg (injected as two ½ doses). It is noted that this study included only 3 animals/dose, rather than the 5 animals/dose recommended in the agency's test guideline (870.5395). In another literature study, Manas *et al.* (2009) reported an induction of micronuclei in BALB/C mice when tested up to 200 mg/kg glyphosate. However, there is some concern regarding how the micronuclei were scored in this study. As stated in the Kier and Kirkland review, Manas *et al.* (2009) reported their findings as an increase in micronucleated erythrocytes rather than polychromatic erythrocytes. Scoring all erythrocytes rather than immature polychromatic erythrocytes can impact the interpretation of the study as the effects cannot be solely attributed to treatment by the test article. Suresh *et al.* (1993) reported an increase in micronuclei in females only in Swiss albino mice treated with 5 mg/kg glyphosate; however, this occurred at a dose that is more than twice the limit dose for the agency's guideline study. Although the above authors reported positive findings, a vast majority of the *in vivo* genotoxicity studies (including the previously reviewed guideline mammalian bone marrow chromosomal aberration test) were negative at doses similar to or higher than the studies discussed above, regardless of the dosing regimen or route of administration. Furthermore, glyphosate was also negative in two rodent dominant lethal tests. A summary of the findings are reported in Table 21.

Table 21. Results from *in vivo* genotoxicity assays[1].

Author	Assay Type	Species/strain	Purity	Highest conc.	Results	Comments
Bolognesi *et al.* (1997)	Micronucleus test	Male mice (strain not provided)	99.9%	300 mg/kg	Positive	Two IP injections of ½ dose; 3 mice/dose
Durward, R. (2006)	Micronucleus test	Young adult male and female albino Crl:CD-1TM(ICR)BR mice	95.7%	600 mg/kg	Negative	Single IP injection; Significant increase in % PCEs per 1000 erythrocytes was observed in the 24-hour; however not 48-hour at 600 mg/kg
Flügge, C. (2009)	Micronucleus test	Male and female CD rats	98.8%	2000 mg/kg	Negative	Single dose; oral gavage
Fox and Mackay (1996)	Micronucleus test	Male and female CD-1 BR mice	95.6%[2]	5000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2005)	Micronucleus test	Male and female NMRI mice	97.73%	2000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2008)	Micronucleus test	NMRI male mice	99.1%	2000 mg/kg	Negative	Single dose; oral gavage
Jensen, J.C. (1991)	Micronucleus test	Young adult male and female NMRI SPF mice	98.6%	5000 mg/kg	Negative	Single dose; oral gavage
Manas *et al.* (2009)	Micronucleus	BALB/C mice	96%	200 mg/kg	Positive	Two IP doses, 1 day apart
NTP (1992)	Micronucleus test	Male and female B6C3F1 mice	99%	11,379 mg/kg/day	Negative	Dietary admin., 13 weeks
Suresh, T.P. (1993)	Micronucleus test	Young Swiss albino male and female mice	98.6%	5000 mg/kg	Males: Negative Females: Positive	Two doses 1 day apart; oral gavage
Suresh, T.P. (1994)	Mouse Bone Marrow Chromosome Aberration	Male and female Swiss albino mice	96.8%	5000 mg/kg	Negative	Two doses, 24 hours apart; oral gavage
Suresh, T.P. (1992)	Rodent dominant lethal test	Male and female Wistar rats	96.8%	500 mg/kg (single dose); 100 mg/kg (5 daily doses)	Negative	
Wrenn (1980)	Rodent dominant lethal test	Mouse; gavage	98.7%	2000 mg/kg	Negative	

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid
3. IP= intraperitoneal injection

5. Other genotoxicity assays

Inconsistent responses were reported in a number of assays designed to detect DNA damage, including sister chromatid exchange (SCE) assay, unscheduled DNA synthesis assay, and the comet assay (also known as the single cell electrophoresis assay). Positive responses in these assays do not necessarily indicate a chemical is DNA-reactive (*i.e.* mutagenic), but rather that DNA damage occurred under conditions of the assay. Glyphosate was also negative in two Rec-DNA repair tests in *B. subtilis*. The results of these genotoxicity studies are presented in Table 22.

Table 22. Additional genotoxicity assays of glyphosate

Authors	Assay Type	Cell Type	Purity	Highest test conc.	Results
Bolognesi *et al.* (1997)	Sister chromatid exchange (SCE)	Human peripheral blood (*in vitro*)	99.9%	1000 ug/mL	Positive
Lioi *et al.* (1998a)	SCE	Human peripheral blood (*in vitro*)	>98%	1.4 mg/L	Equivocal
Lioi *et al.* (1998b)	SCE	Bovine peripheral blood (*in vitro*)	>98%	2.9 mg/L	Equivocal
Li and Long (1988)	Unscheduled DNA synthesis (UDS)	Rat hepatocytes (*in vitro* exposure)	98%	0.125 mg/mL	Negative
Rossberger,(1994)	UDS	Primary rat hepatocytes	98%	111.69 mM	Negative
Bolognesi *et al.* (1997)	DNA Damage /reactivity/UDS	Mouse; IP administration	99.9%	300 mg/kg	Equivocal
Bolognesi *et al.* (1997)	DNA Damage/reactivity/UDS	Mouse; IP; alkaline solution of extracted DNA	99.9%	300 mg/kg	Positive
Alvarez-Moya et al. (2014)	Comet assay	Human lymphocytes	96%[2]	700 µM	Positive
Lueken *et al.* (2004)	Comet assay	Human fibroblasts GM 5757	98.4%	75 mM	Negative
Manas *et al.*(2009)	Comet assay	Liver Hep-2 cells	96%	7.5 mM	Positive
Mladinic et al. (2009)	Comet assay	Human lymphocytes	98%	580 ug/mL (toxic); approximately 3.43 mM	Positive
Rossberger, S. (1994)	DNA repair test	Male SD rat primary hepatocytes	>98%	111.69 mM	Negative
Akanuma, M. (1995)	DNA repair test (Rec- assay)	*Bacillus subtilis* M45 rec-/ H17 rec+	95.68%[2]	240 ug/disk	Negative
Li and Long (1988)	DNA repair test (Rec assay)	*B. subtilis* H17, rec+; M45, rec-	98%	2 mg/disk	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

6. Conclusions

In summary, glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronuclei or chromosomal aberration studies considered in this assessment by the CARC. Some positive results were reported in SCE and comet assays in the open literature; however, there is no convincing evidence that the DNA damage is a direct effect of glyphosate exposure, but rather may be secondary to cytotoxicity or oxidative damage.

C. Structure-Activity Relationship

At present there are no structurally related pesticides registered by the agency which resemble glyphosate. Sulfosate, the trimethylsulfonium salt of glyphosate (also known as glyphosate-trimesium) is a 1:1 molar salt of N-(phosphonomethyl) glycine anion (PMG) and the trimethylsulfonium cation (TMS). Sulfosate was evaluated for its carcinogenic potential following dietary administration to male and female mice at 0, 10, 1000 or 8000 ppm (equivalent to 0, 16, 159 or 1341 mg/kg/day, respectively) for 18 months, and in male and female Sprague-Dawley rats at 0, 100, 500, or 1000 ppm (equivalent to 0, 5.4, 27 or 557 mg/kg/day, respectively) for two years. There was no evidence of carcinogenicity in either species. Sulfosate is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans" based on the absence of carcinogenicity in mice and rats in two acceptable studies. Based on the available mutagenicity studies, there is no concern for mutagenicity (TXR Nos. 0006452 and 0011156).

D. Subchronic and Chronic Toxicity Studies

1. Subchronic Toxicity

In a 90-day feeding study (MRID No. 00036803) CD-1 mice were fed diets containing 0, 250, 500 or 2500 mg/kg/day of glyphosate for three months. Body weight gains of the high-dose males and females were about 24% and 18% lower, respectively, than those of the controls. Body weight gains of the low-dose and mid-dose groups were comparable to those of the controls. For systemic toxicity, the NOAEL is 500 mg/kg/day and the LOAEL is 2500 mg/kg/day, based on decreased body weight gain in both sexes.

In a 90-day feeding study (MRID No. 40559401), Sprague-Dawley rats were fed diets containing 0, 63, 317, and 1267 mg/kg/day of glyphosate, respectively in males and 0, 84, 404 and 1623 mg/kg/day of glyphosate, respectively, in females. Treatment-related findings were: (1) increased serum phosphorus and potassium in all treated groups, males and females; (2) increased serum glucose in the mid-dose and high-dose males; (3) increased blood urea nitrogen (BUN) and serum alkaline phosphatase in the high-dose males; and (4) occurrence of pancreatic lesions in the high-dose males (pancreas was not examined at the low-dose and mid-dose groups). Based on these findings, the systemic NOAEL is <1000 ppm (not determined definitively) for both sexes.

2. Chronic Toxicity

(i) Rats

A chronic feeding/carcinogenicity study (MRID No. 00093879) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 30, 100, or 300 ppm of glyphosate for 26 months. These levels were equivalent to 0, 3, 10, and 34 mg of glyphosate/kg/day, respectively. There were no effects based on any of the parameters examined (toxic signs, mortality, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights and organ/tissue pathology). Therefore, the NOAEL for systemic toxicity is 300 ppm (males: 31 mg/kg/day and females: 34 mg/kg/day).

A second chronic feeding/carcinogenicity study (MRID No. 41643801) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 2000, 8000, or 20,000 ppm of glyphosate for two years. These levels were equivalent to 0, 89, 362, or 940 mg/kg/day, respectively, for the males and 0, 113, 457, or 1183 mg/kg/day, respectively, for the females. Treatment-related effects observed only in the high-dose group included: (1) decreased body weight gain in females; and (2) increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight, and increased liver weight/brain weight ratio (relative liver weight) in males. No significant systemic effects were observed in the low-dose and mid-dose male and female groups. Therefore, the NOAEL for systemic toxicity is 8000 ppm (males: 362 mg/kg/day and females: 457 mg/kg/day) and the LOAEL is 20,000.

In a combined chronic toxicity/carcinogenicity study (MRID No. 49631701), glyphosate (98.9% a.i.) was administered to 85 Sprague-Dawley rats/sex/dose in the diet for 104 weeks ater 0, 10, 100, 300, and 1000 mg/kg/day to both sexes over the course on the study. Designated for the toxicity portion of the study were 35 rats/sex/dose with the remainder designated for the oncogenicity portion of the study. There were no statistical differences between treated and control groups in survival rates. Pale feces were observed during weeks 16–104 in both sexes at the high dose and in females from the low-mid and high-mid dose levels. No treatment-related effect was observed in food consumption, hematology, ophthalmology, and gross pathology data. Males from the high-dose group had statistically lower mean body weight ($P \leq 0.01$) by 5% to 11% beginning Week 2 of the study until Week 104, and at termination was 10% lower (-14% weight gain). Females at the high dose had statistically lower body weight ($P \leq 0.05$) by 5% to 12% beginning Week 20 through Week 80 (with several exceptions), and at termination was 8% lower (-11% weight gain). Statistically increased ALP activities (+46% to +72%) were observed in males at the high dose throughout the study except for the 51 week interval when the mean value was 31% higher than control. Elevated ALP activities were observed in females at the high dose (+34% to +53%) throughout the study, and through most of the study at the high-mid dose by +20% to +67%, though not always statistically significant. Urinalysis data showed reduced pH (5.5–6) in males at the high dose throughout the study.

The absolute liver weight was decreased significantly in females at the high dose after 52 weeks, but after correcting for final body weight the difference was statistically significant at the three highest doses. The parotid salivary gland weight was increased significantly in males at the three highest doses (56–111%) after 52 weeks, but not after 104 weeks. The combined weight of the sublingual and submaxillary salivary glands was significantly increased by 13% (22% after correcting for body weight) at the high dose after 52 weeks. In females, the parotid gland was not affected but the sublingual and submaxillary combined weight was significantly higher by about 15%. The changes in salivary gland weights were accompanied by increased incidence of mild to severe parotid salivary gland cell alterations and slight to moderate mandibular salivary gland cell alterations were observed in both sexes at the 52-week and 104-week intervals. The lesions were described as cells and/or acini that appeared larger and stained in a weakly basophilic manner without showing a tendency toward proliferative or degenerative changes over time. In males, the increased incidence and severity of lesions in the parotid gland were significant ($P \leq 0.01$) at 100, 300, and 1000 mg/kg bw/day at 52 weeks, and significant at 300 and 1000 mg/kg bw/day at 104 weeks. The increased incidence of lesions in the mandibular gland were significant at 300 and 1000 mg/kg bw/day at 52 weeks and significant ($P \leq 0.001$) at 100, 300, and 1000 mg/kg bw/day at 104 weeks. In females, the increased incidence of parotid lesions was significant at 300 and 1000 mg/kg bw/day at 52 weeks, and significant at 100, 300, and 1000 mg/kg bw/day at 104 weeks. The increased incidence in the mandibular gland lesions was significant at the high dose at both 52 and 104 weeks. The incidence and/or severity of kidney nephropathy decreased in males at 100, 300, and 1000 mg/kg bw/day at 52 weeks and at the high dose at 104 weeks. Urothelial hyperplasia significantly decreased in females from the high dose group at both the 52-week and 104-week intervals. The LOAEL in male and female Sprague-Dawley rats administered glyphosate for 104 weeks in the diet was 100 mg/kg bw/day based on microscopic lesions in the parotid and mandibular salivary glands. The NOAEL was 10 mg/kg bw/day (MRID No. 49631701).

In another chronic toxicity/carcinogenicity study (MRID No. 49704601), groups of 52 male and 52 female Alpk:APSD (Wistar-derived) rats were fed diets containing glyphosate at 0, 2000, 6000, or 20,000 ppm for two years. These doses were equivalent to 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437, or 1498 mg/kg/day in females, respectively. Treatment-related findings were confined to the liver and kidneys at the highest dose (20,000 ppm). In both sexes, treatment-related changes manifested as papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, and hematuria. The LOAEL was 20,000 ppm (1214 mg/kg/day in males and 1498 mg/kg/day in females) and the NOAEL was 6000 ppm (361 mg/kg/day in males and 437 mg/kg/day in females)

(ii) Mice

In a carcinogenicity study (MRID No. 00251007), glyphosate (Technical, 99.7% a.i.) was administered to groups of 50 male and 50 female CD-1 mice/sex/dose in the diet at dose levels of 0, 1000, 5000, or 30,000 ppm (approximately equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Cage-side and detailed clinical observations were done. Body weight and food intake were monitored throughout the study. Water consumption was measured during months 12 and 24. Erythrocyte, as well as total

white cell counts and differentials, were done at months 12, 18, and 24. Tissues and organs were collected from all mice whether dying during the study or at terminal sacrifice. Microscopic analyses were done on all collected tissues.

No treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The terminal body weight of high-dose males was significantly decreased 9% while the absolute liver weight of high-dose males was significantly decreased 16%; however, no significant treatment-related effects were found on the liver-to-body-weight ratio. The absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17. Neither were statistically significant, and no microscopic histological correlates were found. The incidences of centrilobular hepatocyte hypertrophy were slightly, but not significantly increased in high-dose male mice. Centrilobular hepatocyte necrosis was significantly higher in high-dose males (10/50** (20%) vs. control 2/49 (4%), $P \leq 0.01$). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice; however, proximal tubular epithelial basophilia was significantly increased in high-dose females (9/50 (18%) vs control 0/50 (0%), $P \leq 0.01$). No other microscopic treatment-related effects were found. Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for males and 6069 mg/kg bw/day for females). The NOAEL for the study was 835 mg/kg bw/day for males and 968 mg/kg bw/day for females) (MRID No. 00251007).

In another carcinogenicity study (MRID No. 49631702), glyphosate (97.5–100.2% a.i.) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. Mortality, body weight, body weight gain, and food consumption were monitored throughout the study. WBC differential counts were done during Weeks 52, 77, and 102 of the study. Organ weights were measured and tissues collected for microscopic analyses. Treatment of male and female mice for 104 weeks did not increase mortality and did not decrease body weight, body weight gain or food consumption. No treatment-related clinical signs of toxicity were observed and no effects were found on WBC differential counts. Treatment did increase the absolute and relative thymus weights of male and female mice treated with 300 or 1000 mg/kg bw/day approximately 2–3-fold, but only the results of male mice were statistically increased. However, no treatment-related effects were found microscopically. At necropsy, the incidence of lung masses was slightly increased in high-dose male mice, but were considered coincidental. Microscopically, there was a slight, but statistically significant increase in mineral deposition in the brains of mid- and high-dose male mice. A non-significant increase was observed in female mice. Kidney cysts were also slightly but statistically increased in low- and mid-dose males, but no increase of cortical tubular eosinophilic droplets was found in female mice. The significance of these findings is questionable since they did not follow a dose-response. The systemic NOAEL for glyphosate in male and female CD-1 mice treated up to 104 weeks was 1000 mg/kg bw/day. A LOAEL was not identified (MRID No. 49631702).

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

A. Evidence for Carcinogenicity in Humans

The CARC evaluated one cohort study and seven nested case-control studies based on the cohort study population and twenty-five case-control studies that examined the association between glyphosate exposure and one or more cancer outcomes.

1. Cancer at Multiple Sites

Several case-control studies reported no association for cancer of the oral cavity, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, breast or melanoma from exposure to glyphosate (De Roos *et al.*, 2005; Engle *et al.*, 2005; Lee *et al.*, 2007; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010).

In single case-control studies, no associations were found for cancers of the esophagus, stomach, prostate or soft-tissue sarcoma from exposure to glyphosate (Alavanja *et al.*, 2003; Lee *et al.*, 2004; Band *et al.*, 2011; Pahwa, *et al.*, 2011; Koutros *et al.,* 2013). No association for childhood cancer was found from maternal or paternal exposure to glyphosate (Flower *et al.*, 2004).

2. Brain Cancer

A case-control study in Nebraska and the Upper Midwest Health case-control study in Iowa, Michigan, Minnesota and Wisconsin did not find any no association of glyphosate with adult brain cancer, specifically for gliomas (Ruder *et al.*, 2004; Carreon *et al.*, 2005; and Lee *et al.*, 2005).

3. Leukemia

No significant association with leukemia was reported in a case-control study in Iowa and Minnesota (Brown *et al.*, 1990) or in the AHS cohort (De Roos *et al.*, 2005). A Swedish case-control study reported a non-statistically significant elevated risk for hairy cell leukemia. However, the authors stipulated that this risk should be interpreted with caution since it was based on only 4 glyphosate-exposed cases (Nordstrom *et al.*, 1998).

4. Multiple Myeloma

No significant association for multiple myeloma from exposure to glyphosate was found in three separate population-based case-control studies: one in Iowa and Minnesota (Brown *et al.*, 1993) and the other in Iowa and North Carolina, USA (De Roos *et al.*, 2005; Sorhan 2015); and the third study in Canada (Pahwa *et al.*, 2012; Kachuri *et al.*, 2013), and in a hospital-based case-control study in France (Orsi *et al.*, 2009). A cohort study found no association with glyphosate exposure and monoclonal gammopathy of undetermined significance, a pre-clinical marker of multiple myeloma progression (Landgren *et al.*, 2009).

5. Non-Hodgkin Lymphoma

There is conflicting evidence for an association between glyphosate exposure and NHL; seven case-control studies reported no association in the U.S, Canada, and France, while two case-control studies from Sweden reported positive association.

No association between glyphosate exposure and NHL was found in four population-based case-control studies in the United States: in Iowa and Minnesota (Cantor *et al.*, 1992); in Iowa, Nebraska and Minnesota (Lee *et al.*, 2004a); in Iowa, Nebraska, Minnesota and Kansas (De Roos *et al.*, 2003) and in the AHS cohort with 57,311 licensed pesticide applicators in Iowa and North Carolina (De Roos *et al.*, 2005).

Similarly, no association between glyphosate exposure and NHL was seen in two population-based case-control studies conducted in various Canadian provinces (McDuffie *et al.*, 2001; Hohenadel *et al.,* 2011).

A hospital based case-control study from France did not find an association between glyphosate exposure and NHL (Orsi *et al.*, 2009).

The first report of an association between glyphosate exposure and NHL was in a population-based case-control study from Sweden (OR=23.3; 95% CI=0.40–13.0); however, this finding was based on only 4 glyphosate-exposed cases and 3 controls (Hardell and Erickson, 1999).

In a 2002 follow-up study, data from two case-control studies in Sweden, one on NHL and the other on hairy cell leukemia, were pooled and analyzed. A univariate analysis showed an increased risk (OR=3.04; 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, risk declined (OR=1.85; 95% CI=0.55–6.20) (Hardell *et al.*, 2002).

In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analyses showed a statistically significantly increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51) (Erickson *et al.*, 2008).

A meta-analysis of the six studies (De Roos *et al.,* 2003; 2005; McDuffie *et al.*, 2001; Hardell *et al.*, 2002; Erickson *et al.*, 2008; and Orsi *et al.*, 2009) that showed an association between glyphosate exposure and NHL, resulted in a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014).

In an attempt to address the noted power/sample size issues and after considering the adjusted estimates of the two Swedish studies, IARC performed a meta-analysis of the data and estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65) (IARC, 2015).

In summary, the epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and non-solid tumors: leukemia, multiple myeloma or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate exposure and NHL. Multiple case-control studies and one prospective cohort study found no association with NHL; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data. The CARC recognizes the meta-analysis conducted by IARC to try to address the power/sample size issues. However, given the limitations of the studies used, a different weighting scheme could easily change the meta-risk ratio. Thus, while the epidemiologic literature to date does not support causal association, the CARC recommends that the literature continue to be monitored for studies related to glyphosate and risk of NHL.

B. Evidence for Carcinogenicity in Experimental Animals

1. Evidence for Carcinogenicity in Rats

A total of seven chronic toxicity/carcinogenicity studies in Wistar or Sprague-Dawley strain rats were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 3.0 mg/kg/day to 1500 mg/kg/day for 2-years.

(i) Testes

In Sprague-Dawley rats (MRID No. 00093879), there was a non-dose-related increase in the incidences of interstitial cell tumors in the testes of males at 3 mg/kg/day (6%), 10 mg/kg/day (2%) and 30 mg/kg/day (12%; P=0.013) when compared to controls (0%). The CARC reaffirmed the previous conclusion that these tumors are not treatment related based on the following considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5; range, 3.4% to 6.7%;) and 5) this finding is not replicated in the other studies in the same strain of rats (*i.e.*, no interstitial cell tumors were seen when tested up to 1100 mg/kg/day). The CARC concluded that the interstitial cell tumors are not treatment-related.

(ii) Pancreas

Benign pancreatic islet cell tumors were seen in male Sprague-Dawley rats in two studies. In the first study (MRID No. 00093879), there was no dose response or statistical significance; the incidences for adenomas were: 0%, 10%, 4% and 4% at the control, low, mid, and high dose groups. Carcinomas were seen in one rat at the high dose. In the second study (MRID No. 41643801), there was a statistically significant increase in adenomas at the lowest (100 mg/kg/day) and the highest (1000 mg/kg/day) doses compared to controls: lowest dose, 8/45 (18%; P=0.018); intermediate dose, 5/49 (10%); and highest dose, 7/48 (15%; P=0.042) versus controls, 1/43 (2%). The CARC reaffirmed the previous conclusion that the benign pancreatic islet cell tumors are not treatment-related due to lack of dose-response, absence of pre-neoplastic lesions, lack of progression to malignancy, and incidences within the historical control range (0–17%) reported for this tumor in this strain of rats. This neoplasm was not seen in the other five studies. The CARC concluded that the pancreatic islet tumors are not treatment-related.

(iii) Liver

In male Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of hepatocellular adenomas (P=0.016). The CARC concluded that the minimal increase in adenomas is not treatment-related due lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions, no progression to malignancy, and the incidences were within the historical control range (1.4–18.3%) of the testing laboratory.

In male Wistar rats (MRID No. 49704601), there was a statistically significant trend (P=0.00804) and pairwise significance for the increase in hepatocellular adenomas at the highest (1214 mg/kg/day) dose compared to controls: lowest dose, 2/52 (4%); intermediate dose, 0/52 (0%); and highest dose, 5/52 (10%; P=0.02826) versus controls, 0/52 (0%). The CARC concluded that this increase is not attributable to treatment based on the following considerations: 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the historical control range (0–11.5%).

The CARC noted that survival was better at the high dose (25/52; 13%) compared to the controls (16/52; 8.3%) which could be reason for the slightly higher incidence (5/52) of age-related background tumors like liver adenomas in the absence of any associated lesions. Furthermore, with a weak genotoxic effect one would expect to see an effect on carcinomas (or at least adenomas/ carcinomas, combined) and shorter latency period, which were not observed in this study. With a weak cytotoxic or mitogenic effect one would expect to see an increase in foci and other non-neoplastic lesions. In addition, as discussed above, only a linear trend (no pairwise) was seen for this tumor type in another strain (Sprague-Dawley) for rats where the incidences were still within the historical control range. Also, liver tumors were not seen in the other four studies. This provides additional evidence for lack of an actual carcinogenic response in the liver. The CARC concluded that the liver tumors are not treatment-related.

(iv) Thyroid

In Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of thyroid C-cell tumors in females (P=0.031). The CARC concluded that the minimal increase is not treatment-related due to lack of statistical significance in pairwise comparison, no progression to carcinomas, no increase in severity of grade or incidence of hyperplasia, and the incidences were within the historical control range (3.3–10%). The CARC concluded that the thyroid tumors in female rats are not treatment-related.

In summary, dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female Sprague-Dawley or Wistar rats.

2. Evidence for Carcinogenicity in Mice

Four carcinogenicity studies in CD-1 mice were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 85 mg/kg/day to 4800 mg/kg/day for 18–24 months. In one study there were no statistically significant or otherwise notable increases in the occurrence of any tumor types. Tumors observed in the other three studies are discussed below.

(i) Kidney

Kidney (renal tubular) tumors were seen in male CD-1 mice in one study (MRID No. 00251007). The incidences of adenomas was 1/49 (2%), 0/49 (0%), 0/50 (0%), and 1/50 (2%) in the control (0 mg/k/day), low- (157 mg/kg/day), mid- (814 mg/kg/day) and high-dose (4945 mg/kg/day) groups, respectively. The incidence of carcinomas was 0/49 (0%), 0/49 (0%), 1/50 (2%) and 2/50 (4%) in the control, low-, mid- and high-dose groups, respectively. The incidence of adenomas or carcinoma (combined) was 1/49 (2%), 0/50 (0%), 1/50 (2%), and 3/50 (6%) in the control, low-, mid-, and high-dose groups, respectively. None of these differences showed statistical significance.

The CARC reaffirmed the previous conclusion that the kidney tumors are not treatment-related based on the following weight-of-evidence considerations: a) lack of dose-related trend or statistical significance in pairwise comparisons; b) lack of non-neoplastic renal tubular lesions (*e.g.* tubular necrosis/regeneration, hyperplasia, or basophilia); c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well; and d) the difference in incidence between high-dose group (3/50) and the control group (1/49) was minimal, especially considering the very high concentration given (4 x time the limit dose).

Furthermore, the Pathology Work Group concluded that the renal tumors were not treatment-related since none of the treatment groups differed from the controls for a linear trend or pairwise statistical significance, there was no treatment-related nephrotoxic lesions including pre-neoplastic changes, and multiple renal tumors were not seen in any animal.

In addition, the CARC noted that renal tumors were not observed when tested at a similar dose (4348 mg/kg/day) in this strain of mice in another study(Arysta, 1997b) or in two other studies at the limit dose (MRID No. 49631702, Nufarm, 2009b). If really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000 – 4000 mg/kg/day.

(ii) Lung adenocarcinoma

There was a dose-dependent increase in the incidence of bronchiolar-alveolar adenocarcinoma of the lung in male CD-1 mice (Nufarm, 2009b). There was a positive trend (P=0.02906) in the incidence of lung adenocarcinomas: 5/51 (10%), 5/51 (10%), 7/51 (14%) and 11/51 (22%) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related due to lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions in the lung (*e.g.*, bronchiolar-alveolar hyperplasia), and incidences in all treated groups within the background range (1.42–26%) for this tumor in this strain and age of mice. Also, lung tumors were not seen when tested at a comparable dose (1000 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other three studies (MRID Nos. 00251007; 49631702; Arysta, 1997b).

(iii) Lymphoma/Lymphosarcomas

There was a dose-dependent and statistically significant increase in the incidence of malignant lymphomas in male mice (Nufarm, 2009b). The incidence was: 0/51 (0%; trend P=0.006633), 1/51 (2%), 2/51 (4%) and 5/51 (10%; P=0.02820) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related since the incidences in the concurrent controls (0%) were not representative of the normal background incidences noted in the historical controls (mean, 4.5%; range, 1.5% to 21.7%), and the apparent statistical significance of the pairwise comparison of the high dose group with the concurrent control might have been attributable to this factor rather than an actual carcinogenic response. Also, this neoplasm was not seen in other studies in this strain of mice. For example, in the study by Knezevich and Hogan 1983 (MRID No. 00251007), there was no significant difference in the incidence of lymphomas between control and high-dose groups (P=1.00 for males, P=0.12 for females). In the study by Atkinson *et al.* (1993) (MRID No. 496317), the incidence values in "lymphoreticular/ hematopoietic tissue" were not significantly different between control and high-dose groups (males: 4 in controls, 6 in high-dose group; females: 14 in controls, 13 in high-dose group). In the Arysta 1997 study (Greim *et al.*, 2015), the incidence of lymphoma in males was 2/50, 2/50, 0/51, 6/50 in the control, low, mid and high dose groups, respectively. There were no statistically significant pairwise differences observed in any of these studies.

(iv) Hemangioscarcomas

Hemangiosarcomas were seen in multiple organs including, liver, spleen, and prostate in males and liver and uterus in female CD-1 mice (MRID No. 49631702). There was a positive trend (P=0.00296) in the incidence of hemangiosarcomas in male mice: 0/47 (0%), 0/46 (0%), 0/50 (0%) and 4/45 (9%) at the 0, 100, 300 and 1000 mg/kg/day groups, respectively. The hemangiosarcomas were present in the liver, spleen or prostate in the high dose males. In females, this neoplasm was seen in one female at the low dose (uterus) and in one high dose (spleen). The CARC did not consider the hemangiosarcomas in males to be treatment-related based on the following considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed in mice as spontaneous tumors and are generally more common in males in CD-1 strain mice; 5) there was not a significant increase in hemangiosarcomas seen in the other three mouse studies; and 6) if really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000-4000 mg/kg/day.

In summary, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female CD-1 mice.

C. Discussion

When determining the carcinogenic potential of chemicals, the IARC identifies a cancer "hazard" if an agent (*e.g.*, chemical) is capable of causing cancer under some circumstance and the agent is termed "carcinogenic" if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The IARC also considers that there is "*sufficient evidence of carcinogenicity"* based on the occurrence of increased tumors (benign, malignant, or combination) in: 1) two or more species of animals; 2) two or more independent studies in one species; and/or 3) an increased incidence of tumors in both sexes of a single species. Furthermore, a single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites (IARC Preamble, 2006).

In March 2015, the IARC evaluated the carcinogenic potential of glyphosate. The IARC determined that there was a positive trend in the incidence of a rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. Thus, in accordance with one of the preamble criteria, "the occurrence of tumors in two studies in one species," IARC determined that there is "sufficient evidence" in experimental animals for the carcinogenicity of glyphosate (IARC, 2015).

In contrast, the USEPA's carcinogenicity classification is based on weight-of-evidence considerations in accordance with the agency's 2005 Guidelines for Carcinogen Risk Assessment. The cancer guideline emphasizes the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. This evaluation is accomplished in a single integrative step after assessing all of the individual lines of evidence. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiological studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insight into the possible mode(s) of action and likelihood of human cancer hazard and risk (USEPA, 2005).

Conclusions for evidence of carcinogenicity are based on the combined strength and coherence of inferences appropriately drawn from all of the available information. The following observations add significance to the tumor findings: tumors in multiple species, strains, or both sexes; dose-related increases; progression of lesions from pre-neoplastic to benign to malignant; proportion of malignant tumors; reduced latency of neoplastic lesions; and both biological and statistical significance of the findings (USEPA, 2005).

The IARC attributed the kidney tumors observed in male CD-1 mice at the high dose in the feeding study (MRID No. 00251007) to treatment since they are rare and there was borderline significance in trend test (P=0.034 for carcinoma and P=0.037 for combined adenoma or carcinoma) in a Cochran-Armitage trend test. However, as shown in Table 14, the agency's statistical analyses did not show a significant trend for either carcinoma (P=0.06345) or the combined adenoma or carcinoma (P=0.06483). In a Fisher's exact test, when compared to the concurrent control, there was no pairwise significance for any tumor type (adenoma, carcinoma, or combined). There were no pre-neoplastic renal tubular lesions such as tubular necrosis/ regeneration, hyperplasia or hypertrophy, despite a high dose level (4945 mg/kg/day) that was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guidelines. Examination of multiple sections of kidneys from all animals by more than one pathologist did not result in any additional neoplasms. Although the highest dose tested (4945 mg/kg/day) was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guideline, the incidence of the kidney tumors was minimal (1/50 adenomas and 2/50 carcinomas) compared to controls (1/49 adenomas). An evaluation by the PWG concluded that the renal tumors are not treatment-related since there were no compound related nephrotoxic lesions, including pre-neoplastic changes, multiple tumors were not found in any animals, and there was no evidence of a significant linear trend at the 0.5 level in a one-tailed Cochran-Armitage test or pairwise significance in a Fisher's exact test. Furthermore, kidney tumors were not seen when tested at lower (85 to 1000 mg/kg/day) doses or at a comparable (4116 mg/kg/day) dose in this strain of mice in the other three studies. Thus, the totality of data available from 4 carcinogenicity studies provides a strong support for the conclusion that the kidney tumors seen in one study is not the result of a carcinogenic response to glyphosate.

The IARC attributed the hemangiosarcomas observed in male CD-1 mice at the high dose in separate feeding study (MRID No. 49631702) to treatment due to the positive trend (P<0.001) in a Cochran-Armitage trend test. As shown in Table 16, the agency's statistical analyses also showed a positive trend (P=0.00296) in the trend test. In the Fisher's exact test, there was no pairwise significance when compared to controls. In contrast with the IARC, the CARC did not consider the hemangiosarcomas to be treatment-related based on the following weight-of-evidence considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed as spontaneous tumors in male CD-1 strain mice; and 5) hemangiosarcomas were not seen when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other studies (MRID No.00251007, Arysta, 1997b, Nufarm, 2009b). It is noted that JMPR in their evaluation also concluded that the hemangiosarcomas are not treatment-related owing to lack of dose-response relationship, lack of statistical significance and incidences within the historical control range (JMPR, 2004).

Hemangiosarcomas have similar histopathological features in rodents and humans but differ in both incidence and tissue site. In human populations, hemangiosarcomas have an incidence rate of approximately 0.2 new cases/100,000 people (0.0002%) (1996–2000, US National Cancer Institute–SEER Database) and account for <1% of all human sarcomas. The historical background incidence of hemangiosarcomas in B6C3F1 and CD-1 mice relative to the incidence rate in humans has thus been estimated to be approximately 10,000-fold higher than in people (Pegg *et al.,* 2012). The most common sites for spontaneous hemangiosarcomas in rodents are liver, spleen, bone marrow, and to a lesser extent in lymph nodes and skin (see references in Pegg *et al.* (2012). In male mice, liver and spleen tend to be the most common sites. Human hemangiosarcoma is most commonly reported in skin (Weiss *et al.*, 2001). Primary liver hemangiosarcoma in humans has been linked to chemical exposure, notably thorotrast and vinyl chloride, which are both considered genotoxic carcinogens. There are several examples of induction of hemangiosarcomas by non-genotoxic agents in mice, but no clear examples of hemangiosarcoma induction by non-genotoxic agents in human populations (Cohen *et al.,* 2009). Several studies have looked at potential mode of action (MOA) for these tumors in mice in response to various drugs or chemicals. These MOAs generally relate to hypoxia or vascular toxicity as early key events.

1. Mutagenicity

Glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronucleus assay studies. There is no convincing evidence that the DNA damage is a direct effect of glyphosate, but under some conditions may be secondary to cytotoxicity or oxidative damage. Furthermore, the chemical structure of glyphosate, with its absence of alkyl groups also provides SAR support for the lack of mutagenic/genotoxic potential.

IARC concluded that "there is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic"; however, the IARC analysis included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e.*, no purity information was provided). The CARC did not include such studies in their evaluation. The IARC analysis also focused on DNA damage as an endpoint (*e.g.*, comet assay); however, DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited, where positive findings were reported for chromosomal damage, had study limitations confounding the interpretation of the results. In addition, these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. This includes many negative studies cited by Kier and Kirkland (2013) that were considered by CARC, but were not included in the IARC decision.

2. Structure Activity Relationship

Sulfosate (the trimethylsulfonium salt of glyphosate) is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans," based on the lack of evidence of carcinogenicity in mice and rats in two acceptable studies, and absence of mutagenicity concern.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, glyphosate is classified as "Not Likely to be Carcinogenic to Humans." This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at

doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Not required.

VIII. BIBLIOGRAPHY

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To: Dix, David[Dix.David@epa.gov]
From: Jones, Jim
Sent: Thur 11/5/2015 2:39:20 PM
Subject: FW: materials for Tom B glyphosate meeting
417300_2015-10-01_TXR0057299.pdf
TB Brief Glyphosate JR 11 3 15.pptx

In case you haven't seen. Jim

From: Mojica, Andrea
Sent: Tuesday, November 03, 2015 12:19 PM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>
Subject: materials for Tom B glyphosate meeting

Jim,

Attached are the materials for the Tom B glyphosate briefing. The relevant cancer slides from your briefing last week and the glyphosate CARC document from October 1, 2015. OK to send to ORD?

Thanks,

Andrea

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **October 1, 2015**

SUBJECT: **GLYPHOSATE:** Report of the Cancer Assessment Review Committee

PC Code: 417300
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: NA
TXR No.: 0057299
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS No.: 1071-83-6
40 CFR: N/A

FROM: Jess Rowland,
Deputy Division Director
Chair, Cancer Assessment Review Committee
And
Karlyn Middleton, Co-Chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Charles Smith, Chief,
Risk Assessment Branch I
Health Effects Division (7509P)
And
Khue Nguyen
Chemical Review Manager
Risk Management and Implementation Branch 1
Pesticide Re-evaluation Division

On September 16, 2015, the Cancer Assessment Review Committee (CARC) of the Health Effects Division, of the Office of Pesticide Programs evaluated the carcinogenic potential of Glyphosate in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
Glyphosate

FINAL REPORT
October 1, 2015

CANCER **A**SSESSMENT **R**EVIEW **C**OMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S Environmental Protection Agency

Table of Contents

COMMITTEE MEMBERS IN ATTENDANCE:

Jess Rowland, M.S., Chair

Karlyn Middleton, M.S., Co-Chair

Gregory Akerman, Ph.D.

Lori Brunsman, B.S.

Jonathan Chen, Ph.D.

Anwar Dunbar, Ph.D.

Ray Kent, Ph.D.

Jessica Kidwell, M.S.

John Liccione, Ph.D.

Dannelle Lobdell, Ph.D., Epidemiologist, ORD

Nancy McCarroll, M.S.

Chris Schlosser, M.S.

Charles Wood D.V.M., Ph.D., Pathologist, ORD

EXECUTIVE SUMMARY

Glyphosate is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops.

In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division (HED), of the Office of Pesticide Programs (OPP), of the U.S. Environmental Protection Agency (USEPA) evaluated the carcinogenic potential of glyphosate. In accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* the CPRC classified glyphosate as a Group E Chemical: "Evidence of Non-Carcinogenicity for Humans" based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR# 0008897).

Earlier this year (March 2015), the International Agency for Research on Cancer (IARC), Lyon, France, assessed the carcinogenic potential of glyphosate. The IARC reviewed the available epidemiological studies and carcinogenicity studies for glyphosate in experimental animals. The IARC concluded that there is *limited evidence* in humans for the carcinogenicity of glyphosate based on a positive association for non-Hodgkin lymphoma (NHL). The IARC also concluded that there is *sufficient evidence* in experimental animals based on significant positive trends for kidney tumors in one study and for hemangiosarcomas in another study in male mice. IARC determined that there is strong evidence for genotoxicity. Overall, IARC classified glyphosate as "*probably carcinogenic to humans (Group 2A)* (IARC, 2015).

IARC's conclusion was based on epidemiologic studies available in the open literature and carcinogenicity studies in rats (4 studies) and mice (2 studies) by dietary administration. Of these six studies reviewed by IARC, two studies in rats and one study in mice were previously not available to OPP. The conclusion by IARC and the additional studies not available to OPP, prompted the agency to re-evaluate the carcinogenic potential of glyphosate.

On September 16, 2015, HED's Cancer Assessment Review Committee (CARC) evaluated all available epidemiological studies published in the open literature that examined the association between glyphosate exposure and one or more cancer outcomes. This included one cohort study, seven nested case-control studies based on the cohort study population, and 25 case- control studies. The CARC also evaluated 11 chronic toxicity/carcinogenicity studies in rats (7) and mice (4) following dietary administration for up to two years. Six of the studies (4 rat and 2 mouse) were submitted to OPP to support registration/re-registration requirements, including two studies in rats and one study in mice which were not previously available to OPP (but reviewed by IARC). Data for review of the other five studies (3 rat and 2 mouse) were obtained from a review article and its supplement published in the open literature (Greim *et al.,* 2015) that also had not been previously reviewed by the agency (IARC did not evaluate the five studies cited in the Greim *et al.* 2015 review article). The CARC also evaluated the mutagenicity/genotoxicity studies submitted to OPP as well as studies summarized in two review articles (Williams *et al*., 2000, and Kier and Kirkland, 2013) published in the open literature.

The CARC concluded that the epidemiological studies in humans showed no association between glyphosate exposure and cancer of the following: oral cavity, esophagus, stomach, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, brain (gliomas), soft-tissue sarcoma, leukemia, or multiple myelomas.

The CARC concluded that there is conflicting evidence for the association between glyphosate exposure and NHL. No association between glyphosate exposure and NHL was found in population-based case-control studies in the United States, Canada or France. Additionally, the large prospective Agricultural Health Study (AHS) with 54,315 licensed pesticide applicators in Iowa and North Carolina did not show a significantly increased risk of NHL. A population-based case-control study from Sweden suggested an association between glyphosate exposure and NHL; however, this finding was based on only 4 glyphosate-exposed cases and 3 controls.

When data from two case-control studies in Sweden (one on NHL and the other on hairy cell leukemia) were pooled, a univariate analysis showed an increased risk (odds ratio (OR) = 3.04; 95% confidence interval (CI) = 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, the risk was attenuated (OR=1.85; 95% CI=0.55–6.20). In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analysis showed an increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51). A meta-analysis of the six separate studies showed an association between glyphosate exposure and NHL with a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014). The CARC noted that most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and had risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data.

In an attempt to address the noted power/sample size issues across studies, IARC used adjusted weighting estimates of the two Swedish studies (Hardell *et al*. 2002 and Eriksson *et al*. 2008) and

reported an lower odds ratio in a second meta-analysis of the same data (OR=1.3; 95% CI=1.03–1.65). Given the limitations of the studies used and uncertainty in the analytical methods, the CARC concluded that a different weighting scheme could have resulted in a different meta risk ratio. Thus, while epidemiologic literature to date does not support a direct causal association, the CARC recommends that the literature should continue to be monitored for studies related to glyphosate and risk of NHL.

Overall, the CARC concluded that there was no evidence of carcinogenicity in the eleven carcinogenicity studies conducted in Sprague Dawley or Wistar rats and CD-1 mice. There were no treatment-related increases in the occurrence of any tumor type in either sex of either species.

By contrast, the IARC concluded that there is *sufficient evidence* in experimental animals based on a positive trend in the incidence of a relatively rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in CD-1 males in one feeding study. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. The CARC did not consider these tumors to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported non-neoplastic changes, were not statistically significant on pairwise analysis with concurrent control groups, and/or were within the range of the historical control data. If the kidney tumors and the hemangiosarcomas are really treatment-related, it is unlikely that the same tumors would not have been detected at higher incidences in the studies in the other studies of CD-1 mice when tested at similar or higher doses (1000–4000 mg/kg/day). Moreover, in 4 of the 11 studies (3 rat and 1 mouse) evaluated by CARC, there was no biologically or statistically significant increases in the occurrence of any tumor type in either species. The other observed differences in incidence did not show a dose response relationship, and were within the range of the background/historical control range. The four studies which were negative for carcinogenicity were reported in the review article by Greim *et al.* (2015) but were not included in the IARC evaluation. This omission of the negative findings from reliable studies may have had a significant bearing on the conclusion drawn for evidence of carcinogenicity in animals.

The CARC evaluated a total of 54 mutagenicity/genotoxicity studies which included studies submitted to the agency, as well as studies reported in the two review articles (Williams *et al.*, 2000, and Kier and Kirkland, 2013). A number of studies reported in the review article by Kier and Kirkland (2013) were not considered by IARC. The CARC, based on a weight-of-evidence of the *in vitro* and *in vivo* studies, concluded that there is no concern for genotoxicity or mutagenicity. Glyphosate was no mutagenic in bacterial reversion (Ames) assays or *in vitro* mammalian gene mutation assays. There is no convincing evidence that glyphosate induces micronuclei formation or chromosomal aberrations *in vitro* or *in vivo*.

By contrast, IARC's conclusion that glyphosate is genotoxic based on positive results that included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e.*, no purity information was provided). The IARC analysis also focused on DNA damage as an endpoint (*e.g.*, comet assay). DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA

changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited as positive findings for chromosomal damage had deficiencies in the design and/or conduct of the studies confounding the interpretation of the results. In addition these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. Furthermore, IARC's evaluation did not include a number of negative results from studies that were reported in the review article by Kier and Kirkland (2013). The inclusion of the positive findings from studies with known limitations, the lack of reproducible positive findings and the omission of the negative findings from reliable studies may have had a significant bearing on IARC's conclusion on the genotoxic potential of glyphosate.

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, based on the weight-of-evidence, glyphosate is classified as "Not Likely to be Carcinogenic to Humans". This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk/odd ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis with concurrent control groups, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

I. INTRODUCTION

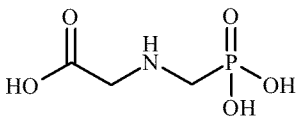
On September 16, 2015 the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of glyphosate.

II. BACKGROUND INFORMATION

Glyphosate (*N*-(phosphonomethyl) glycine) is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops. Tolerances are currently established for residues of glyphosate in/on various plant commodities at 0.2–400 ppm (40 CFR §180.364 (a)) (1). Registered uses range from tree nuts, citrus, and grapes to corn, soybeans, cotton, and rice. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Aquatic and terrestrial registered uses of glyphosate include non-selective control of nuisance aquatic weeds, ornamentals, greenhouses, residential areas, ornamental lawns and turf, fallow land, pastures, and nonagricultural rights-of-way.

The chemical structure and nomenclature for glyphosate is presented in Table 1.

Table 1. Chemical Nomenclature of Glyphosate

Compound	
Common name	Glyphosate
Company experimental name	DPX-B2856
IUPAC/CAS name	*N*-(phosphonomethyl)glycine
CAS registry number	1071-83-6

Glyphosate is formulated in liquid and solid forms, and it is applied using ground and aerial equipment. Application rates of glyphosate to food crops range from <1 pound (lb) of acid equivalent (ae) per acre (A) for a variety of crops to approximately 15 lb ae/A for spray and spot treatments of crops including tree nuts, apples, citrus, and peaches. Residential lawn and turf application rates range from <1 lb ae/A to approximately 10.5 lb ae/A. The application timing of glyphosate is varied. Glyphosate can be applied early and late in the season, at pre-plant, planting, pre-emergence, pre-bloom, bud stage, pre-transplant, pre-harvest, post-plant, post-transplant, post-bloom, and post-harvest. It can also be applied during dormant stages and to fallow land, established plantings, stubble, and when needed. In September 1993, the agency issued the glyphosate Reregistration Eligibility Decision (RED) document (D362745), available from http://www.epa.gov/pesticides/reregistration/REDs/old_reds/glyphosate.pdf.

In 1985, the agency, in accordance with the Proposed Guidelines for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical (Possible Human Carcinogen) based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No. 0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical: Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). This review is available at http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division, Office of Pesticide Programs, in accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* classified glyphosate as a Group E Chemical: Evidence of Non-Carcinogenicity for Humans. This classification was based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR No. 0008897).

In 2002, the European Union (EU) concluded that there was no evidence of carcinogenicity for glyphosate in long-term studies with mice and rats (EU, 2002).

In 2004, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that there was no evidence of carcinogenicity for glyphosate in long term studies in mice and rats and there was no evidence for genotoxic potential (JMPR, 2004).

In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as a Group 2A chemical (Probable Human Carcinogen) based on *limited evidence* of carcinogenicity in humans and sufficient evidence in experimental animals. The limited evidence in humans was based on a positive association between non-Hodgkin lymphoma (NHL) and glyphosate exposure from published epidemiology studies. The *sufficient evidence* in experimental animals was based on a positive trend in the incidence of renal tubular carcinoma and renal tubule adenoma/ carcinoma combined in male CD-1 mice in one study and on a positive trend in the incidence of hemangiosarcomas in male CD-1 mice in another study. There is strong evidence that glyphosate causes genotoxicity (IARC, 2015).

In 2015, two chronic toxicity/carcinogenicity studies in rats (MRID Nos. 49631701; 4970460) and one carcinogenicity study in mice (MRID No. 49631702) that were reviewed by IARC, but not previously available to OPP, were submitted and reviewed. This assessment by the CARC includes all of the studies (epidemiology and animals) reviewed by IARC as well as a subset of animal studies reported in a review article by Greim *et al.* (2015) but not reviewed by IARC.

III. EPIDEMIOLOGY

This section includes a review of epidemiologic cohort and case-control studies of glyphosate to evaluate whether exposure to glyphosate is associated causally with the risk of developing cancer in humans.

The Agricultural Health Study (AHS) is a large prospective study conducted in Iowa and North Carolina. Participants (private and commercial applicators) were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying pesticides (including glyphosate), and frequency (days of use per year) and duration (years of use) of pesticide use. Data on the use of personal protective equipment, other farming practices, dietary and lifestyle information, demographic data, and medical information were also collected via the questionnaire (Alavanja *et al.,* 1996). The role of pesticide use and lymph hematopoietic cancers, and in particular NHL, has been studied in several investigations. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available (De Roos *et al.*, 2005); however, for NHL and other non-solid tumors, several investigations are published.

A. Cohort Study

There are multiple published studies which use data from the same cohort, the AHS (Alavanja *et al.,* 2003; Flower *et al.*, 2004; De Roos *et al.*, 2005; Engel *et al.*, 2005; Lee *et al.*, 2007; Landgren *et al.*, 2009; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010). It should be noted that there is some overlap between the cases and person-time reported findings in the AHS.

B. Case-Control Studies

Three case-control studies conducted by the National Cancer Institute in Iowa and Minnesota during the 1980s were reported by Brown *et al.* (1990), Cantor *et al.* (1992) and Brown *et al.* (1993).

De Roos *et al.* (2003) and Lee *et al.* (2004a) reported the results of case-control studies conducted in Iowa, Minnesota, Nebraska and/or Kansas in the U.S.A.

The Canadian population based case-control studies were reported by McDuffie *et al.*, 2001; Hohenadel *et al.*, 2011; Karunanayke *et al.*, 2012; and Kachuri *et al.*, 2013.

Results of the Swedish case-control studies were reported by Nordstrom *et al.*, 1998; Hardell and Erikson, 1999 and Hardell *et al.*, 2002; and Eriksson *et al.*, 2008.

A single case-control study conducted in France was reported by Orsi *et al.* (2009).

Coco *et al.*, (2013) reported the results of a pooled analyses of case-control studies conducted in six European countries between 1998 and 2004.

Case-control studies on the cancer of the brain (mainly gliomas) were reported by Ruder *et al.* 2004; Carreon *et al.*, 2005; Lee *et al.*, 2005; and Yiin *et al.*, 2012.

Case-control studies on other cancer sites were reported by Alavanja *et al.*, 2004 (lung); Bank *et al.*, 2011 and Koutros *et al.*, 2013 (prostate); Pahwa *et al.*, 2012 (soft tissue sarcoma) and Lee *et al.,* 2004b (stomach and esophagus).

Schinasi and Leon (2014) conducted a meta-analysis of the six studies that evaluated NHL and glyphosate exposure (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; DeRoos *et al.*, 2003; 2005; Eriksson *et al.*, 2008; and Orsi *et al.*, 2009). Sorahan (2015) conducted a re-analysis of the multiple myeloma in the U.S. AHS.

C. Results

A summary of the studies evaluating the association between glyphosate exposure and cancer are discussed below.

- Results of the studies reporting data on solid tumors (non-lymphohematopoietic) at various anatomical sites are presented in Table 2.

- Results of the studies reporting data on glyphosate exposure and non-solid tumors (lymphohematopoietic) are presented in Table 3.

1. Solid Tumor Cancer Studies

Within the AHS study cohort, a number of authors evaluated several anatomical cancer sites in relation to pesticide use. A discussion of studies outside of the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in Section C.2. (Non-Solid Tumor Sites).

(i) Cancer at Multiple Sites

De Roos *et al.*, (2005) evaluated associations between glyphosate exposure and cancer incidence in the AHS cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. The authors used Poisson regression to estimate exposure-response relationships between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Exposure to glyphosate was not associated with all cancers combined [Rate Ratio (RR) =1.0 with 95% Confidence Interval (CI) of 0.90–1.2)] or any cancer at a specific anatomical site.

Several AHS nested case-control analyses as well as the cohort analysis from De Roos *et al.*, 2005, also provide information concerning the carcinogenic potential of glyphosate. As presented in Table 2, there is no statistical evidence of an association with glyphosate presented across these studies. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and cancers of the oral cavity (De Roos *et al.*, 2005), colon (De Roos *et al.*, 2005; Lee *et al.*, 2007), rectum (De Roos *et al.*, 2005; Lee *et al.*, 2007), lung (De Roos *et al.*, 2005), kidney (De Roos *et al.*, 2005), bladder (De Roos *et al.*, 2005), pancreas (De Roos *et al.*, 2005; Andreotti *et al.*, 2009), breast (Engel *et al.*, 2005), prostate (Alavanja *et al.*, 2003; Koutros *et al.*, 2013) or melanoma (De Roos *et al.*, 2005; Dennis *et al.*, 2010). The risk ratios (OR) or rate ratios (RR) and 95% confidence interval (CI) for these studies are provided in Table 2.

In a population-based study (Band *et al.*, 2011) outside of the AHS, Canadian researchers reported non-significantly elevated odds of prostate cancer in relation to glyphosate use (OR=1.36; 95% CI=0.83–2.25). This study included prostate cancer cases from 1983-1990, prior to the prostate-specific antigen (PSA) era. Consequently, the study included more advanced tumors before diagnosis. Additionally, these data are in conflict with the results of Alavanja *et al.* (2003), which reflects the PSA-era cases (*i.e.*, cases which are typically identified at an earlier stage in the progression of the disease). Koutros *et al.* (2013) did not identify an association with advanced prostate cancer (OR=0.93; 95% CI=0.73–1.18) in a prostate cancer follow-up study within the AHS.

A Canadian case-control study (Pahwa *et al.*, 2011) examined exposure to pesticides and soft tissue sarcoma and found no relation with the use of glyphosate (OR=0.90; 95% CI= 0.58–1.40).

Flower *et al.* (2004) examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with maternal use exposure to glyphosate (OR=0.61; 95% CI= 0.32–1.16) or paternal (prenatal) exposure to glyphosate: (OR=0.84; 95% CI= 0.35– 2.54).

(ii) Brain (Glioma) Cancer

Lee *et al.* (2005) investigated the association between brain cancer with farming and agricultural pesticide use. The authors conducted telephone interviews of men and women diagnosed with gliomas (n=251) between 1988 and 1993 in Nebraska and in controls (n=498) identified from the same regions. Matching for age and vital status, study authors reported a non-significant elevated odds of glioma (OR=1.5; 95% CI=0.7–3.1) in relation to glyphosate use; however, the results were significantly different between those who self-reported pesticide use (OR=0.4; 95% CI=0.1–1.6), and for those for whom a proxy respondent was used (OR=3.1; 95% CI=1.2–8.2), indicating recall bias was likely a characteristic of this study.

Three population-based case-control studies evaluated the risk of brain cancer, specifically, glioma risk, among men and women participating in the Upper Midwest Health Study (Carreon *et al.*, 2005; Ruder *et al.*, 2004; Yiin *et al.*, 2012). Ruder *et al.* (2004) reported no association between brain cancer and glyphosate use, but did not present any specific results (*i.e.* quantitative data). Among glioma cases identified 1995–1997 by Carreon *et al.* (2005), the authors found little evidence of a role for glyphosate in the etiology of this tumor. Herbicide use, including glyphosate was not associated with glioma in women by proxy respondents (OR=0.75; 95% CI=0.4–1.3) or excluding proxy respondents (OR=0.6; 95% CI=0.3–1.2). In the study by Carreon *et al.* (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to Lee *et al.* (2005). Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), the authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (home and garden use: OR=0.98; 95% CI=0.67–1.43; non-farm jobs: OR=0.83; 95% CI=0.39–1.73) (Yiin *et al.*, 2012).

(iii) Stomach and Esophageal Cancers

In a population-based case control study in eastern Nebraska, Lee *et al.* (2004) investigated pesticide use and stomach and esophageal adenocarcinomas. Cancer cases (stomach=170 and esophagus=137) were identified through the state cancer registry, and confirmed by a pathologist. The exposure assessment was based on self-reported pesticide use, with follow-up telephone interview to verify the reported information. There was no association between glyphosate exposure and either stomach cancer (OR=0.8; 95% CI=0.4–1.5) or esophageal cancer (OR=0.7; 95% CI=0.3–1.4).

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Cancer at Multiple Sites					
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	All cancers RR =1.0 (0.9-1.2)	No association between glyphosate exposure and all cancer including NHL	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)
Site-Specific Cancers: Lung; Oral cavity; Colon; Rectum; Kidney; Bladder; Prostate and Melanoma					
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	Lung RR= 0.9 (0.6-1.3) Oral Cavity RR=1.0 (0.5-1.8) Colon RR=1.4 (0.8-2.2) Rectum RR=1.3 (0.7-2.3) Pancreas RR=0.7 (0.3-2.0) Kidney RR=1.6 (0.7-3.8) Bladder RR=1.5 (0.7-3.2) Prostate RR=1.1 (0.9-1.3) Melanoma RR=1.6 (0.8-3.0)	No significant association between glyphosate exposure and cancer of the lung, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate or melanomas	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Breast Cancer					
Engel *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 30,454 wives of licensed pesticide applicators with no history of breast cancer at enrollment	Self-report questionnaire	Direct exposure (wives who applied) OR=0.9 (0.7-1.1) (Exposed: 82 cases, 10,016 controls) Indirect exposure (wives whose husbands applied) OR=1.3 (0.8-1.9) (Exposed: 109 cases, 9,304 controls)	No association between glyphosate exposure and breast cancer	Age, race and state of residence (Iowa and North Carolina). Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Pancreatic Cancer					
Andreotti *et al.* (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; follow-up to 2004 93 cases 82,503 controls	Self-report questionnaire; validated, reliability tested	Ever-use OR=1.1 (0.6, 1.7) (Exposed: 55 cases)	No association between glyphosate exposure and pancreatic cancer	Age, smoke, diabetes, applicator type. Limited to licensed applicators. Potential exposure to multiple pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Prostate Cancer					
Alavanja *et al.* (2003) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997; cancer thru 1999 55,332 male applicators	Self-report questionnaire; validated, reliability tested	No quantitative risk estimate reported	No quantitative estimate due to lack of significant exposure-response association with prostate cancer.	Age, family history. Limited to licensed applicators. Potential exposure to multiple pesticides
Band *et al.* (2011) British Columbia, Canada	Case-Control 1983- 1990 1,516 prostate cancer patients 4,994 age-matched controls	Job exposure matrix for agriculture; detailed occupational history; exposure aggregated over all jobs reported. 60 exposed cases	OR=1.36 (0.83-2.25) (Exposed: 25 cases 60 controls)	No association between glyphosate exposure and prostate cancer	Alcohol consumption, cigarette years, education level, pipe smoking years and respondent
Koutros *et al.* (2013) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2003 1,962 incident cases, including 919 aggressive prostate cancers among 54,412 applicators	Self-report questionnaire, validated	OR=0.93 (0.73-1.18)	No association between glyphosate exposure and prostate cancer	Age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Colorectal Cancer					
Lee *et al*. (2007) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-97; follow-up to 2002 56,813 licensed pesticide applicators	Self-report questionnaire	Colon OR=1.0 (0.7-1.5) (Exposed: 151 cases 49 controls) Rectum OR=1.6 (0.9-2.9) (Exposed: 74 cases 18, controls) Colorectal OR=1.2 (0.9-1.6) (Exposed: 225 cases 67 controls)	No significant association between glyphosate exposure and colon, rectum or colorectal cancer	Age, smoking, state, total days use pesticides. Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Cutaneous Melanoma					
Dennis *et al.* (2010) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 150 cases, 24,554 non-cases	AHS self-report questionnaire	No quantitative risk estimate reported	No quantitative estimate due to lack of an association with cutaneous melanoma	Age, sex, tendency to burn, red hair, sun exposure time, BMI at 20 years

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Site-Specific Cancers: Soft Tissue Sarcoma					
Pahwa *et al.* (2011) Canada	Case-Control 1991-1994 342 cases, 1506 age/resident matched controls	Self-reported use, structured interview/ questionnaire; cumulative exposure (+/-10 days/yr)	OR=0.90 (0.58-1.40)	No association between glyphosate exposure and soft tissue sarcoma	Significant medical history variables and with strata for the variables of age group and province of residence
Total Childhood Cancer					
Flower *et al.* (2004) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control; hybrid prospective/ retrospective 1993-1998 21, 375 children of licensed pesticide applicators In Iowa (n=17,357) North Carolina (n=4018)	Self-report questionnaire; duration and frequency of pesticide use; Female Family questionnaire (child name)	<u>Maternal use</u> OR=0.61 (0.32-1.16) 32 cases <u>Paternal use (prenatal)</u> OR=0.84 (0.35-2.34);	No association was detected between frequency of parental pesticide application of glyphosate and childhood cancer risk.	Potential exposure to other pesticides. Child age in multiple logistic [standardized incidence ratio (SIR)] was unadjusted

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Brain Cancer (Glioma)					
Lee *et al.* (2005a) Nebraska	Population based Case-Control study 1988-1993; 251 glioma cases 498 controls	Self-reported questionnaire information, telephone follow-up for unclear responses; men and women assessed separately	Self-Report OR=0.4 (0.1- 1.6) (Exposed: 4 cases 17 controls) Overall OR=1.5 (0.7-3.1) (Exposed: 17 cases 32 controls) Proxy report OR=3.1 (1.2- 8.2) (Exposed:13 cases 15 controls)	Non-significant excess risk for the overall group, but inconsistent for self-report and proxy indicating recall bias	Age, proxy, respond type
Ruder *et al.* (2004) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin, U.S.A.)	Population-based Case-Control 1995-1997 457 glioma cases 648 population controls	Self-report questionnaire, with telephone based follow-up	No quantitative risk estimate reported for glyphosate.	No association with glyphosate exposure and brain cancer	Farm residence, age, use of other pesticides

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Carreon *et al.* (2005) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 341 glioma cases, 528 controls	Self-report questionnaire	Proxy respondents OR=0.75 (0.4-1.3) (Exposed: 18 cases 41 Controls) Excluding proxy OR=0.6 (0.3-1.2) (Exposed:10 cases)	No association with glyphosate exposure and brain cancer	Age, education and use of other pesticide
Yin et al. (2012) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case-Control 1995-1997 798 glioma cases 1,175 controls	Self-report questionnaire	Home/garden use OR=0.98; 95% CI=0.67 - 1.43; Non-farm jobs: OR=0.83; 95% CI=0.39-1.73)	No significant positive association with glyphosate exposure and brain cancer	Age, sex, education and use of other pesticide

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR) / Odds Ratio (OR) (95% Confidence Interval CI)**	**Conclusions**	**Potential Confounders Considered**
Esophagus and Stomach Cancer					
Lee *et al*. (2004b) Nebraska, U.S.A.	Population based Case-Control 1988-1993 137 esophageal cases; 170 stomach cases; 502 controls	Self-report pesticide use, telephone structured interview	Esophagus OR=0.7 (0.3-1.4) (Exposed:12 cases 46 controls) Stomach OR=0.8 (0.4-1.5) (Exposed: 12 cases 46 controls)	No association with glyphosate exposure and esophagus or stomach cancer	Age, sex

2. Non-Solid Tumor Cancer Sites

A number of studies evaluating the possible link between pesticide use and lymphohematopoietic cancers such as leukemia, multiple myeloma and NHL are presented in Table 3.

(i) Leukemia

In a population-based case-control study in Iowa and Minnesota, Brown *et al.* (1990) investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR=0.9; 95% CI=0.5–1.6). The study population (578 cases; 340 living and 238 deceased and 1245 controls) was identified from cancers reported to state registry or authorities in 1981–1984, and the pesticide exposure assessment was performed through in-person interviews which the authors state likely reduced the exposure misclassification (*i.e.* incorrect exposure information). Although the large sample size is a strength of this study, the limitations include not controlling for exposure to other pesticides, limited power for studying the effects of glyphosate use, and the potential for recall bias.

In a Swedish population-based case-control study, 121 cases in men and 484 controls matched for age and sex were identified in 1987–1992 through the Swedish cancer registry. The authors reported a non-statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR=3.1; 95% CI=0.8–12.0), controlling for age, sex, and residential location. However, because these results are based on only 4 glyphosate-exposed cases and 5 exposed controls as noted by the authors, this risk should be interpreted with caution. Also, there was limited power to detect an effect and there was no adjustment for other exposures. At this time, there is limited available literature concerning glyphosate use and leukemia (Nordstrom *et al.*, 1998).

(ii) Multiple Myeloma

In a follow-up analyses using the same study population from Iowa and Minnesota Brown *et al.* (1993) investigated whether pesticide use is also related to multiple myeloma. Among men in Iowa (173 cases, 605 controls), the authors observed a statistically non-significant elevated association with glyphosate use (OR=1.7; 95% CI=0.8–3.6). However, the authors caution that while the study may lend support to the role of pesticides in general, the study limitations preclude use of the evidence as a definitive finding for any one compound.

De Roos *et al.* (2005) reported a suggestive association between multiple myeloma and glyphosate-exposed pesticide applicators based on a small number (32) of cases. For applicators with the full data set (54,315) and without adjustment for other variables the OR was 1.1; 95% CI=0.5–2.4. In the fully adjusted model, there was a non-statistically significantly elevated risk (OR=2.6; 95% CI=0.7–9.4), however, the number of participants included in this analysis was lower (n=40,716) due to missing data for the covariates. The authors postulated that the increased myeloma risk could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses.

Sorahan (2015), using Poisson regression, re-analyzed the AHS data reported by De Roos *et al.* (2005) to examine the reason for the disparate findings in relation to the use of a full data set versus the restricted data set. Risk ratios were calculated for exposed and non-exposed subjects. When adjusted for age and sex, the OR was 1.12 with the 95% CI of 0.5–2.49 for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of other pesticides did not have any effect (OR=1.24; 95% CI=0.52–2.94).

In a population-based case-control study among men in six Canadian provinces between 1991 and 1994, researchers reported non-statistically significantly elevated odds of multiple myeloma in relation to glyphosate use (OR=1.22; 95% CI=0.77–1.93), based upon 32 glyphosate exposed multiple myeloma case and 133 controls (Pahwa *et al.*, 2012).

Kachuri *et al.* (2013), using the same Canadian study population as above, further explored multiple myeloma in relation to days per year glyphosate used in 342 cases of multiple myeloma and 1357 controls. For ever use, the OR=1.19 and 95% CI=0.76–1.87. For light users (≤2 days/year) there was no association (OR=0.72; 95% CI=0.39–1.32; 15 exposed cases); whereas, for heavy users (>2 days/ year), there was a non-significant increased odds ratio (OR=2.04; 95% CI=0.98–4.23; 12 exposed cases). The limitation in this study was the same as the previous study (*i.e.*, the number of cases and controls exposed to glyphosate were very low).

Landgren *et al.* (2009), within the AHS study population, investigated the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS). The MGUS is considered a pre-clinical marker of multiple myeloma progression. The authors did not observe a link with glyphosate use in the AHS cohort (OR=0.50; 95% CI=0.20–1.0).

(iii) Lymphoma

The National Cancer Institute (NCI) performed a series of population-based case-control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred non-Hodgkin lymphoma (NHL) cases and controls, the identified cases were through disease registries which in many cases, were histopathologically confirmed. The investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time.

Cantor *et al.* (1992), in a case-control study of NHL interviewed a total of 622 white men and 1245 population based-controls in Iowa and Minnesota. Only 26 cases and 49 controls ever handled glyphosate yielding an OR of 1.1 with the 95% CI of 0.7–1.9. The study, however, did not adjust for exposure to other pesticides.

De Roos *et al.* (2003) used pooled analysis (n=3,417) of three case-control studies of NHL conducted in white men in Nebraska, Kansas and in Iowa and Minnesota. Based on 36 exposed cases and 61 exposed controls, the risk estimates for the association between glyphosate exposure and NHL was significant (OR=2.1; 95% CI=1.1–4.0) in the logistic regression analyses. However,

utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, there was an increase risk, but the increase was not statistically significant (OR=1.6; 95% CI=0.90–2.8). Overall, the data showed a suggestive association.

Based on the above findings, Lee *et al*., (2004) examined the relationship between asthma and pesticide exposure, and NHL. Pooling data from several midwestern states (IA, MN, and NE) increased the study sample size, and additional pesticide use information was incorporated to adjust the risk estimate (duration and frequency of use, telephone follow-up interview). The study included 872 men with NHL and 2381 frequency-matched controls. The authors reported that the OR associated with glyphosate was not statistically significantly different among those with asthma (OR=1.2; 95% CI=0.4–3.3; 6 exposed cases) and among those without asthma (OR=1.4; 95% CI=0.98–2.1; 53 exposed cases), adjusting for age, state and vital status.

The three studies discussed above (Cantor *et al*., 1992; De Roos *et al*., 2003 and Lee *et al*., 2004) reflect the same population in the AHS and used different levels of information (duration and frequency of exposure) and different analytic techniques [hierarchical regression and stratified analysis (by atopy)]. While studies with increasing levels of refinement to methodology report a stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

A population-based case–control study (Hardell and Erickson, 1999) investigated the exposure to pesticides as a risk factor for NHL in Sweden during 1987–1990. Exposure data were ascertained by comprehensive questionnaires and supplemented by telephone interviews. Of the 404 cases and 741 controls, only 4 glyphosate-exposed cases and 3 controls were included in the study. In a univariate analysis, the risk estimate was elevated, but precision was low (OR=2.3; 95% CI=0.40–13.0).

Hardell *et al*. (2002) analyzed pooled data from two case-control studies from Sweden that examined NHL (Hardell and Erickson, 1999) and another on hairy cell leukemia, a subtype of NHL (Nordstrom *et al*., 1998). In the univariate analysis glyphosate exposure was found to be significantly increased (OR=3.04; 95% CI=1.08–8.52) but, when study site, and vital status were considered in a multivariate analyses, there was a non-statistically elevated risk among glyphosate users (OR=1.85; 95% CI=0.55–6.20). However, the wide range of the CI suggest that the study is under powered and, therefore the findings do not allow definitive conclusion on the association of NHL and glyphosate exposure.

In another case-control study in Sweden (1999–2003), Eriksson *et al*. (2008) examined the effects of exposure to different agents and NHL among 910 NHL cases and 1016 non-NHL controls. Glyphosate exposure which was reported in 29 cases and 18 controls produced an OR of 2.02 (95% CI=1.10–3.71) in a univariate analysis and an OR of 1.51 (95% CI=0.77–2.94) in a multivariate analysis conducted to clarify the relative importance of exposure to different pesticides. When exposure was for more than 10 days/year, the OR was 2.36 (95% CI=1.16–4.40)

and for exposure less than 10 days/year, the OR was 1.69 (95% CI=0.7–4.07). The risk estimate was elevated also for B-cell lymphoma and glyphosate exposure (OR=1.87; 95% CI=0.998–3.51).

McDuffie *et al.* (2001) in a multicenter-population based study among men of six Canadian provinces estimated the association between glyphosate and NHL. The study included 517 cases and 1506 controls identified betwen1991and 1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of cases, implemented a two-tiered exposure questionnaire; and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the test results. There was a non-statistically significant increased risk of NHL from glyphosate exposure. The OR was 1.26 and the 95% CI was 0.87–1.80 for 51 exposed cases, adjusted for age and province and the OR was 1.20 with a 95% CI of 0.83–1.74 when adjusted for age, province and high-risk exposure (adjusted for statistically significant medical variables such as history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative).

In a follow-up study which controlled for exposure to other pesticides, the risk to NHL from glyphosate exposure was attenuated. Glyphosate exposure which was reported in 19 cases and 78 controls produced an OR of 0.92 with 95% CI of 0.54–1.55 (Hohenadel *et al.*, 2011). Within this series of studies, the authors also evaluated Hodgkin lymphoma (HL), and observed little statistical evidence of an association, using similar study design and methods. Among the 38 cases exposed to glyphosate the OR was 0.99 with a 95% CI of 0.62–1.56 (Karunanayake *et al.,* 2012).

In a hospital-based case control study conducted between 2000 and 2004 in France, authors identified 491 NHL cases and 456 age-and sex-matched controls, and performed telephone-based questionnaire to assess pesticide and other confounding variables. There was no association between NHL and glyphosate use; for the 12 exposed cases, the OR was 1.0 and the 95% CI was 0.5–2.2). For Hodgkin lymphoma, for the 6 exposed cases, the OR was 1.7 and the 95% CI was 0.6–5.0 (Orsi *et al*., 2009).

The EPILYMPH case-control study was conducted across six countries in Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain) to explore the role of occupational exposure to specific chemicals and risk of lymphoma overall, B-cell lymphoma and other subtypes. Although the study recruited 2348 cases and 2462 controls, only a very small number of cases were exposed to glyphosate (n=4) and controls (n=2). A non-significant increase in OR was observed for B-cell lymphoma (OR=3.1; 95% CI=0.6–17.1), but the estimate is unstable due to the small number of exposed cases and controls (Cocco *et al.,* 2013)

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL using data from six of the above mentioned studies (McDuffie *et al*., 2001; Hardell *et al*., 2002; DeRoos *et al*., 2003 and 2005; Eriksson *et al*., 2008; and Orsi *et al*., 2009). Since the authors identified a variety of sources of heterogeneity between publications, they calculated meta-risk ratio (RR) estimates and 95% CIs using random effect models, allowing between study heterogeneity to contribute to the variance. They reported I^2 values, which represented the

percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency. For glyphosate, the meta-risk ratio was 1.5 with a 95% CI of 1.0–2.0 and the I^2 value was 32.7% indicating greater inconsistency in these data sets. This study combined multiple smaller studies that on their own were very limited in statistical power to detect differences.

The 2015 IARC evaluation noted that fully adjusted risk estimates in two of the Swedish studies (Hardell *et al.*, 2002 and Eriksson *et al.*, 2008) were not used in the analysis conducted by Schinasi and Leon (2014). Consequently, IARC conducted a reexamination of the results of these studies. For an association between glyphosate exposure and NHL, the IARC estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65), I^2=0%; p=0.589 for heterogeneity) (IARC 2015).

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Leukemia					
Brown *et al.* (1990) Iowa and Minnesota, U.S.A.	Population-based Case-Control 1981-1984 578 cases 1245 controls	In person interview; surrogates used.	OR=0.9 (0.5-1.6) (Exposed:15 cases 49 controls)	No association between glyphosate exposure and leukemia	Vital status (alive, dead), residency (IA or MN), tobacco use, parent, sibling, or child with a lymphopoietic cancer, high risk occupation and exposure to substances (benzene, hair dyes etc) related to risk of leukemia
Nordstrom *et al.* (1998) Sweden	Population-based Case-Control 1987-1992 121 cases 484 controls	Self-reported pesticide questionnaire and follow-up telephone interview	OR=3.1 (0.8-12) (Exposed: 4 cases 5 controls)	A non-statistically significant elevated risk of hairy cell leukemia	Age, sex, country of residence (selected using matching, dissolved matching analyses) No adjustment for exposure from other pesticides
Multiple Myeloma					
Brown *et al.* (1993) Iowa, U.S.A.	Population based Case-Control 1981-1984 173cases 650 controls	Interview based questionnaire with follow-up	OR=1.7 (0.8-3.6) (Exposed: 11 cases 40 controls)	Limited power to assess association of glyphosate exposure and multiple myeloma	Age and vital status

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
De Roos *et al*. (2005) Iowa and North Carolina, U.S.A.	Prospective Cohort 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	Full data set RR =1.1 (0.5-2.4) (Exposed: 32 cases) Adjusted for age etc RR=2.6 (0.7-9.4)	No risk for full data set. Excess risk only with no missing information of 22 cases in the restricted data set (Sorahan, 2015)	Missing data on covariates when multiple adjustments were made, limiting interpretation
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=2.4 (0.8-7.3) (Exposed: 5 cases 18 controls)	No significant association with glyphosate exposure and multiple myeloma	Age, center, socioeconomic category
Pahwa *et al*. (2012) Canada	Population based Case-Control 1991-1994 342 cases 1506 controls	Self-reported pesticide use, structured interview with questionnaire; cumulative exposure (+/-10 days/yr)	OR=1.22 (0.77-1.93) (Exposed: 32 cases 133 controls)	No significant association with glyphosate exposure and multiple myeloma	Significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age group and province of residence

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Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Kachuri *et al.* (2013) Canadian Provinces	Population based Case-Control 1991-1994 342 cases 1357 controls	Self-administered questionnaire	For ever use OR=1.19 (0.76-1.87) Exposed: 32 cases 121controls Light (<2 d/yr) use OR=0.72 (0.39 -1.32) Exposed: 15 cases 88 controls Heavy (>2 d/yr) use OR=2.04 (0.98-4.23) Exposed: 12 cases 29 controls	No association with glyphosate exposure and multiple myeloma for ever or light users Increase for heavy users is non-significant	Relatively low response rate
Monoclonal Gammopathy of Undetermined Significance (MGUS)					
Landgren *et al.* (2009) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-1997 678 participants	Self-administered questionnaire	OR=0.5 (0.2-1.0)	No association with glyphosate exposure and MGUS, a premalignant disorder that often precedes multiple myeloma	Age and education

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Non-Hodgkin Lymphoma (NHL)					
Cantor *et al.* (1992) Iowa and Minnesota, U.S.A.	Population based Case-Control 1980-1983 622 cases 1245 controls	Structured interview, questionnaire response; farm activities and specific pesticide use	OR=1.1 (0.7-1.9) Exposed: 26 cases 49 controls	No association with glyphosate exposure and NHL	Vital status, age, state, smoking, family history, high risk occupation, high risk exposure. Not controlled for exposure to other pesticides.
De Roos *et al.* (2003) Iowa, Nebraska, Minnesota, Kansas, U.S.A.	Case-Control 1983-1986\Nebraska 1979-1981\Kansas 1979-1986 870 white male cases 2569 white male controls	Interview-based questionnaire, demographic	Logistic regression OR=2.1 (1.1-4.0) Exposed: 36 cases 61 controls Hierarchical regression OR=1.6; (0.9-2.8)	Significant increased OR in logistic model but in the hierarchical model, the OR attenuated and no significant association with glyphosate exposure and NHL	Age, study site, use of all other pesticides (group); hierarchal regression informed priors based on chemical-specific information
Lee *et al.* (2004a) Iowa, Nebraska, Minnesota, U.S.A	Population based Case-Control 1980-1986 872 white male cases	In person, structured interview (pesticide use, duration, frequency, first and last year used); 5-yr follow-up interview, 10-min telephone on pesticide use	Non-asthmatic OR=1.4 (0.98-2.1) (Exposed: 53 cases 91 controls) Asthmatic OR=1.2 (0.4-3.3) (Exposed: 6 cases 12 controls)	No significant association with glyphosate exposure and NHL either for asthmatics or non-asthmatics	Adjusted for age, vital status, state

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Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A.	Nested Case-Control 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	OR=1.1 (0.7-1.9 (Exposed: 92 cases)	No significant association with glyphosate exposure and NHL	Age, smoking, other pesticides, alcohol consumption, family history of cancer, education
Hardell and Erickson (1999) Sweden	Population based Case-Control 1987-1990 404 male cases 741 male controls	Questionnaire and follow-up interview	Univariate OR=2.3 (0.4-13.0) (Exposed: 4 cases 3 controls) Multivariate OR=5.8 (0.6-54)	Some evidence of a link with glyphosate, matching variables; cannot conclude regarding causal role for any specific pesticide	Age, region, vital status (matching). Few subjects exposed. Variables used in multivariate were no specified. Study has limited power to detect an effect
Hardell *et al.* (2002) Sweden	Population based Case-Control Combined Hardell 1999 with another case-control study examining hairy cell leukemia (one of 61 types of NHL) 1987-1990 515 cases 1141 controls	Questionnaire and follow-up interview	Univariate OR=3.04 (1.08-8.52) (Exposed: 8 cases 8 controls) Multivariate OR=1.85 (0.55-6.20)	Risk attenuates when adjusted for other variables in the multivariate analysis	Age, country, study site, vital status, other pesticide exposure in the multivariate analysis

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Eriksson *et al.* (2008) Sweden	Population based Case-Control 1999-2002 910 cases 1016 controls	Questionnaire and follow-up interview	Univariate OR=2.02 (1.10-3.71) (Exposed: 29 cases 18 controls) Multivariate OR=1.55 (0.77-2.94) With <10 days/ year OR=1.69 (0.7-4.07) (Exposed: 12 cases 9 controls) With > 10 days/year OR=2.36 (1.04-5.37) (Exposed: 17 cases 9 controls) B-cell lymphoma OR=1.87 (0.998-3.51)	Suggestive association for NHL with glyphosate exposure	Age, sex, year of diagnosis. Multivariate analysis adjusted for exposure to other pesticides
McDuffie *et al.* (2001) Canada	Population based Case-Control 1991-1994 517 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	Univariate OR=1.26 (0.87-1.8) (Exposed: 51 cases 133 controls) Multivariate OR=1.20 (0.83-1.74)	No significant association with glyphosate exposure and NHL	Adjusted for statistically significantly medical variables (history of measles, mumps, cancer, allergy shots, and a positive family history of cancer) males only

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Hohenadel *et al.* (2011) Canada	Case-Control 1991-1994 513 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	OR=0.92 (0.54-1.55) (Exposed: 19 cases 78 controls)	No significant association with glyphosate exposure and NHL	Age, province and proxy respondent, males only
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.0 (0.5-2.2) (Exposed: 12 cases 24 controls)	No association with glyphosate exposure and NHL	Age, center, socioeconomic category
Cocco *et al.* (2013) Czech Republic, France, Germany, Italy, Ireland and Spain	EPICLYMPH Case-Control 1998–2003 2348 cases 2462 controls	Occupational exposure; trained interviewers conducted in person interviews with cases and controls	OR=3.1 (0.6-17.1) (Exposed: 4 cases 2 controls)	No significant association with glyphosate exposure and B-cell	Age, center, socioeconomic category
Hodgkin Lymphoma					
Orsi *et al*. (2009) France	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=1.7 (0.6-5.0) (Exposed: 6 cases 15 controls)	No significant association with glyphosate exposure and HL	Age, center, socioeconomic category

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate: Risk Ratio (RR/ Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Karunanayake *et al.,* (2012). Canada	Case-Control 1991-1994 361 cases 1,506 controls	Questionnaire and follow-up interview	Univariate OR=1.14(0.74-1.76) (Exposed :38 133 controls) Multivariate OR=0.99 (0.62-1.56)	No association with glyphosate exposure and HL	History of measles, acne, hay fever, shingles and positive family history of cancer in a first-degree relative

D. Discussion

In epidemiologic studies, the quality of the exposure assessment is a major concern since the validity of the evaluations depends in large part on the ability to correctly quantify and classify an individual's exposure. During their life-time, farmers are typically exposed to multiple pesticides and several of them are used together posing a challenge for identifying specific risk factors. Moreover, there is no direct information on pesticide exposure or absorbed dose because analyses are based on self-reported pesticide use. The studies included in this epidemiology assessment relied primarily on questionnaires and interviews to describe participants' past and/or current exposure to glyphosate. Since the questionnaires are commonly used to account for exposure and capture self-reporting, it can be subject to misclassification and recall bias. For example, case-control studies are at risk of recall bias in the reporting of pesticide use in the past because cases may have spent more time thinking about past exposures than controls. This could lead to differential misclassification and bias relative risk from null. The possible effect of confounding factors, which are related to both the exposure of interest and the risk of disease, may make it difficult to interpret the results. Therefore, the ability of epidemiologic studies to provide convincing evidence of causation under such circumstances may be limited. Causation is suspected if several studies are consistent in their findings and; if the association between the agent and the risk of disease is strong (*i.e.*, high risk ratio). Support from animal data will help to make the case for causation, particularly by establishing biological plausibility and the existence of a potential mechanism. Another important consideration in assessing epidemiologic studies is that commercially formulated products (not the active ingredient) are used by farmers. For example, glyphosate is sold as Roundup®, which is a combination of the active ingredient and other chemicals that often include a surfactant (polyethyleneamine) used to enhance the spreading of spray droplets when they contact the foliage. Thus, it is possible that different glyphosate-containing formulations were used across the different studies.

Most of the studies discussed here were hypothesis-generating in nature, consisted of small sample sizes with limited power to detect associations and evaluated use of glyphosate in addition to several other pesticides and often evaluated risk of multiple different types of cancer. Therefore, the role of chance given the many different statistical tests performed and the lack of a pre-specified hypothesis, limit epidemiologic inference. This hypothesis-generating evidence observed in the studies requires further prospective follow-up studies to determine whether a true association with glyphosate is indeed null. The case-control studies are retrospective studies and are susceptible to recall bias for exposure reporting which could account for discrepancies in the study findings. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could also explain these inconsistencies in the data. In contrast, a prospective cohort study evaluates a number of diseases simultaneously and facilitates performance of periodic assessments of agricultural and other exposures. Periodic assessment of recent exposures enhances recall and reduces non-differential misclassification. The ability to determine exposure prior to the onset of a disease eliminates the case-recall bias, which was an issue identified as a weakness in case-control studies.

IV. EVALUATION OF CARCINOGENICITY IN ANIMALS

A total of 11 chronic toxicity/carcinogenicity studies (7 rat and 4 mouse) were included in this weight of evidence review. Of these, six studies were submitted for review to EPA under the registration/reregistration programs including two studies in rats (MRID No. 496311701 and 49704601) and one in mouse (MRID No. 49631702) not previously reviewed. Data for review of the other five studies were obtained from a published review article by Greim *et al.*, 2015 and were available online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423. The IARC acknowledged the Greim *et al.,* (2015) review article, but did not evaluate the studies cited in the review because the information provided in the review and its supplement was insufficient.

For this assessment, each study reported in the Greim *et al.,* (2015) review article was evaluated in accordance with the agency's 2012 Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf). In accordance with this guidance, the following four studies were not included in this weight of evidence assessment since there is low confidence were determined to be unreliable for carcinogenicity evaluation.

- A two year feeding study in Sprague-Dawley rats (Excel, 1997) was not included due to the lack of test article characterization (no purity of test material).

- The two-year drinking water study in Wistar rats reported by Chruscielska *et al.*, (2000) was not included since the tested material was a formulated product (13.6% ammonium salt) and there were a number of deficiencies (lack of purity, water consumption and body weight data) in the conduct and reporting of the study.

- An initiation-promotion study (George *et al.*, 2010) in male Swiss mice that tested a commercial formulation of glyphosate (41%) with study deficiencies (*e.g.* small number (20) of animals, tested only males, and lack of histopathological examination).

- A carcinogenicity study in Swiss mice (Feinchemie Schwebda, 2001) was not included due to the presence of viral infection within the colony, which confounded the interpretation of the study findings. Malignant lymphomas were reported in this study in all groups. However, lymphomas are one of the most common types of spontaneous neoplastic lesions in aging mice (Brayton *et al.*, 2012). Murine leukemia viruses (MuLVs) are a common cause of lymphoma in many different strains of mice (Ward 2006). Tadesse-Heath *et al.* (2000) reported 50% lymphoma (mostly B-cell origin) incidence in a colony of Swiss mice. Although the incidences in this study were within or near the normal variation of background occurrence, it is not clear whether or not the viral component may have contributed to incidence value reported or the lower survival seen at the high dose in the study. Raw data are not available to perform appropriate statistical analyses of the lymphomas correcting for the intercurrent mortality.

A. Carcinogenicity Studies in Rats

1. Lankas, G, P. A Lifetime Study of Glyphosate in Rats. December 23, 1981. Unpublished report No. 77-2062 prepared by Bio Dynamics, Inc. EPA Accession. No. 247617 – 247621. MRID No. 00093879.

a. Experimental Design

Groups of Sprague-Dawley rats (50/sex/dose) were fed diets containing glyphosate (98.7%, pure) at concentrations of 0, 30, 100 or 300 ppm for 26 months. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in females were maintained.

b. Survival Analysis

There were no treatment-related effects on survival at any dose level.

c. Discussion of Tumor Data

There was an increase in the incidences of interstitial cell tumors in the testes of male rats at the low (3/5; 6%), mid (1/50; 2%) and the high dose (6/50; 12%; P=0.013 pairwise comparison) when compared to controls (0/50; 0%). In 1991, HED's Cancer Peer Review Committee (CPRC) did not consider the increases to be treatment-related based on the following weight of evidence considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5%; range, 3.4% to 6.7%) and 5) no interstitial cell tumors were seen when tested at much higher doses in the same strain of rats in an another study (discussed below). The CARC agreed with the CPRC conclusion and rationale and noted additional rat studies which also showed no effect on interstitial cell tumors.

Although there was no evidence of a treatment-related increase in the incidences of pancreatic islet cell tumors in male rats, the data are presented in Table 4 since this tumor also seen in the second study discussed below.

Table 4. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats (MRID 00093879)				
Tumor Type	0 ppm	30 ppm	100 ppm	300 ppm
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Combined (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

d. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

The CPRC concluded that the highest dose tested was not adequate to assess the carcinogenic potential of glyphosate. Consequently, a second study was conducted (discussed below).

2. Stout, L. D. and Rueckerf, P.A. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; September, 26, 1990, MRID No. 41643801; Historical Controls; MRID No. 41728701.

a. Experimental Design

Groups of Sprague-Dawley rats (60/sex/dose) were fed diets containing glyphosate (96.5%, pure) at dietary concentrations of 0, 2000, 8000 or 20,000 ppm 24 months. These levels were equivalent to 0, 89, 362 or 940 mg/kg/day, respectively, for the males and 0, 113, 457 or 1183 mg/kg/day, respectively, for the females. An interim sacrifice was conducted on 10 rats/sex/dose at 12 months.

b. Discussion of Tumor Data

The most frequently seen tumors were pancreatic cell adenomas, hepatocellular adenomas and thyroid C-cell adenomas in males. Data for these tumors and the respective historical control data are presented in Tables 5 thru 11.

Pancreatic cell adenomas are presented in Table 5 and the historical control data are presented in Table 6. Hepatocellular adenomas seen in males are presented in Table 7 and the historical control data are presented in Table 8. The thyroid C-cell adenomas and/or carcinomas observed in males and females are presented in Tables 9 and 10, respectively, and the historical control data are presented in Table 11.

(i) Pancreas

There was no statistically significant trend test by dose for pancreatic islet cell tumors. Increased incidences of adenomas only were observed at the low- and high-dose groups but not at the mid-dose group.

Table 5. Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas	1/43[a]	8/45	5/49	7/48[b]
(%)	(2)	(18)	(10)	(15)
P =	0.170	0.018*	0.135	0.042*
Carcinomas	1/43[c]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
P=	0.159	0.409	0.467	0.472
Combined	2/43	8/45	5/49	7/48
(%)	(2)	(18)	(10)	(15)
P=	0.241	0.052	0.275	0.108

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 81 in the 20,000 ppm group
c. First carcinoma observed at week 105 in the controls (0 ppm)
* Significant in a pair-wise comparison (P<0.05)

Historical control data on the incidence of pancreatic islet cell adenomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 6.

Table 6. Historical Control Data — Pancreatic Islet Cell Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)

Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Tumor Incidence	2/68	5/59	4/69	1/57	5/60	3/60	3/59
%	2.9%	8.5%	5.8%	1.8%	8.3%	5.0%	5.1%

The CPRC concluded that the pancreatic islet cell adenomas are not treatment-related based on the following weight of evidence considerations: 1) although the incidences at the low (18%) and high (15%) dose groups exceeded the historical control range (1.8–8.5%), there was lack of statistical significance in Cochran-Armitage trend test; 2) the tumor incidence in the concurrent control was at the low end of the historical control range; 3) considerable inter-group variability in the numbers of males with tumors (*i.e.*, no dose-response); 4) there were no preneoplastic changes; 5) there was no progression from adenomas to carcinomas; and 6) the apparent statistical significance of the pairwise comparisons of the treated groups with the concurrent control may be due to the low incidences in the controls and not to an actual carcinogenic response. Furthermore, the incidences of pancreatic cell tumors for the two studies did not show dose-response and the incidences were within the historical control range (0 to 17%) reported in the open literature (Arnold *et al.,* 1985; Borelli *et al.*, 1990; Borzelleca *et al.*, 1986, 1989, 1990; Burnett *et al.*, 1988; Trochimowicz *et al.*, 1988). The CARC agreed with the CPRC conclusion and rationale and noted subsequent rat studies which also showed no effect on islet cell tumors.

(ii) Liver

There was a dose trend for adenomas only. There were no statistically significant increases in the occurrence of benign or malignant hepatocellular tumor types (Table 7). The observed variations in incidence were within the range of the historical control data.

Table 7. Glyphosate: Hepatocellular Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)

Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/44[a] (5) 0.016*	2/45 (4) 0.683	3/49 (6) 0.551	7/48[b] (15) 0.101
Carcinomas (%) P =	3/44 (7) 0.324	2/45 (4) 0.489	1/49 (2) 0.269	2/48[c] (4) 0.458
Adenoma/Carcinoma (%) P =	5/44 (11) 0.073	4/45 (9) 0.486	4/49 (8) 0.431	9/48 (19) 0.245

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 88 in the 20000 ppm group
c. First carcinoma observed at week 85 in the 20000 ppm group

Historical control data on the incidence of hepatocellular adenomas and carcinomas in male Sprague-Dawley rats in 2-year studies (1983–1989) conducted at the testing facility (Monsanto Environmental Health Laboratory; MRID No. 41728701) are presented in Table 8.

Table 8. Historical Control Data : Hepatocellular Adenomas in Male Sprague-Dawley Rats (MRID No. 41728701)							
Study No.	1	2	3	4	5	6	7
Study Year	07/83	02/85	10/85	6/85	9/88	1/89	3/89
Adenomas	5/60 (8.3%)	11/68 16.2%)	1/70 (1.4%)	3/59 (5.1%)	11/60 (18.3%)	5/60 8.3%)	4/60 (6.7%)
Carcinomas	4/60 (6.7%)	0/68 (0%)	1/70 (1.4%)	2/59 (3.4%)	3/60 (5%)	1/60 (1.7%)	0/60 (0%)

The CPRC concluded that the slightly increased incidence of adenomas in male rats are not treatment-related since: 1) the increase was not statistically significant in pairwise comparison with the controls; 2) the incidences were within the historical control range; 3) except for a single animal at the mid-dose late in the study (89 weeks), no hyperplasia, preneoplastic foci or other non-neoplastic lesions were seen; and 4) there was no evidence of progression from adenomas to carcinomas. The CARC agreed with the CPRC conclusion and rationale.

(iii) Thyroid

The increased incidences in C-cell adenomas observed at the mid and high-dose groups of rats of both sexes did not show a statistically significant difference in pairwise comparisons with the controls (Table 9 and 10, respectively). There was a dose trend observed for adenomas and adenomas/carcinomas in females (P=0.03). Historical control data are presented in Table 11.

Table 9. Glyphosate: Thyroid C-Cell Tumors in Male Sprague-Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P =	2/54[a, b] (4) 0.069	4/55 (7) 0.348	8/58 (14) 0.060	7/58 (12) 0.099
Carcinomas (%) p =	0/54 (0) 0.452	2/55[c] (4) 0.252	0/58 (0) 1.000	1/58 (4) 0.518
Adenoma/Carcinoma (%) p =	2/54 (11) 0.077	6/55 (11) 0.141	8/58 (14) 0.060	8/58 (14) 0.060

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 54 in the controls
c. First carcinoma observed at week 93 in the 20,000 ppm

Table 10. Glyphosate: Thyroid C-Cell Tumors in Female Sprague Dawley Rats Cochran-Armitage Trend & Fisher's Exact Test (MRID No. 41643801)				
Tumor Type	0 ppm	2000 ppm	8000 ppm	20000 ppm
Adenomas (%) P=	2/57[a] (4) 0.031*	2/60 (7) 0.671	6/59[b] (10) 0.147	6/55 (11) 0.124
Carcinomas (%) P=	0/57 (0) 0.445	0/60 (0) 1.000	1/59[c] (2) 0.509	0/55 (0) 1.000
Adenoma/Carcinoma (%) p=	2/57 (4) 0.033*	2/60 (3) 0.671	7/59 (12) 0.090	6/55 (11) 0.124

a. Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed prior to study week 55.
b. First adenoma observed at week 72 in the controls
c. First carcinoma observed at week 93 in the 8000 ppm group.

Table 11. Historical Control Data – Thyroid C-cell Tumors in Sprague-Dawley Rats (MRID No. 41728701)		
Tumor Type	Males	Females
Adenomas	1.8 – 10.6%	3.3 – 10.0%
Carcinomas	0.0 – 5.2%	0.0 – 2.9%

The CPRC concluded that the thyroid tumors in either sex are not treatment-related since: 1) the increased incidences exhibited no statistically significant trend or pairwise comparisons with the controls in males; 2) in females, there was a trend but no pairwise significance; 3) there was no progression from adenomas to carcinomas; and 4) there was no dose-related increase in severity of grade or incidence of hyperplasia in males or females. The CARC agreed with the CPRC conclusion and rationale and noted other rat studies which showed no effect on thyroid C-cell tumors.

c. Non-Neoplastic Lesions

There were no treatment-related precursor lesions at any dose level.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was near or beyond the limit dose (1000 mg/kg/day).

3. **Atkinson, C., Strutt, A., Henderson, W., et al. (1993). 104-Week chronic feeding/ oncogenicity study in rats with 52-week interim kill. Inveresk Research International (IRI), Tranent, Scotland. Study No. 438623; IRI Report No. 7867. April 7, 1993. MRID No. 49631701. Unpublished.**

a. Experimental Design

In a combined chronic toxicity/carcinogenicity study, glyphosate (98.9% pure) was administered to 50 male and female Sprague-Dawley rats/sex/dose in the diet at 0, 10, 100, 300, and 1000 mg/kg/day for 104 weeks. An interim sacrifice was conducted on 15 rats/sex/dose after 52 weeks of treatment.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

There were no treatment-related increases in the occurrence of any tumor type in this study.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing was considered to be adequate to assess carcinogenicity since the highest dose tested was the limit dose (1000 mg/kg/day) and at this dose increased salivary gland weight accompanied by cellular alterations in the mandibular and/or parotid glands occurred in both males and females.

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4. **Brammer. (2001). Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Rats. Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK: Syngenta. (MRID No. 49704601).**

a. Experimental Design

In a combined chronic toxicity study, glyphosate acid (97.6% pure) was administered to groups of Wistar rats in the diet. Groups of 52 male and 52 female rats received diets containing 0, 2,000, 6,000, and 20,000 ppm glyphosate for 24 months. The achieved doses were 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437 or 1498 mg/kg/day in females, respectively. Three satellite groups of 12 rats/sex/group were also included for

interim sacrifice at 12 months of treatment. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested

c. Discussion of Tumor Data

As shown in Table 12, there was an increase in the incidence of hepatocellular adenomas in male rats at the high dose when compared to controls. This increase was not considered to be treatment-related due to 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the range (0–11.5%) of historical controls for this strain (Wistar) of rats in 26 studies conducted during the relevant time period (1984–2003) at the testing laboratory; and 5) the 0% incidence in concurrent controls is lower than the average background incidence for liver adenomas in male Wistar rats.

Table 12. Liver Adenomas in Male Wistar Rats Fisher's Exact Test and Exact Trend Test Results

	0	2000	6000	20000
Adenomas	0/52[a]	2/52	0/52	5/52
(%)	(0)	(4)	(0)	(10)
P =	0.00804**	0.24757	1.00000	0.02826*

a =Number of tumor-bearing animals/Number of animals examined.

In addition, statistically higher survival (P=0.02) was observed in males at 20,000 ppm at the end of 104 weeks relative to controls, and an overall trend for improved survival was observed in treated males (P=0.03). The inter-current (early) deaths were 37/52, 36/52, 35/52, and 26/52 for the control, low, mid and high dose groups, respectively. The terminal deaths were 16/52, 17/52, 18/52, and 26/52 for the control, low, mid and high dose groups, respectively. This survival bias in the high dose group could easily explain a modestly higher incidence of an age-related background tumor like liver adenoma (and fits with lack of associated lesions). In the 1990 study in Sprague-Dawley rats (MRID No. 41643801) there was also a weak but significant trend test for liver adenomas in males (P=0.02, no pairwise); however, in that study adenomas in all treatment groups were still within the historical control and the CPRC concluded that this effect was not treatment-related, as discussed above. The lack of increased liver tumor incidence in the other rat studies provide additional evidence for lack of an actual carcinogenic response in the liver.

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in any organs of either sex at any dose level tested.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes (1214 mg/kg/day in males and 1498 mg/kg/day in females) exceeded the limit dose (1000 mg/kg/day). Treatment-related findings at these doses were observed in the liver and kidney, notably renal papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, hematuria and slight increases in the incidence of proliferative cholangitis and hepatitis.

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5. Feinchemie Schwebda. (1996). Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats. Bangalore, India: Rallis India, Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (96.0-96.8% pure) was administered to groups of Wistar rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 100, 1000, and 10000 ppm glyphosate for 24 months. The average achieved doses were 0, 7.4, 73.9, and 740.6 mg/kg/day. Parameters evaluated included clinical signs, body weights, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy, and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no non-neoplastic lesions at any dose level in either sex.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The doses tested were determined to be adequate in both sexes since the highest dose tested (741 mg/kg/day) approached the limit dose (1000 mg/kg/day).

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6. Arysta Life Sciences. (1997a). HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015).

a. Experimental Design

In a combined chronic/carcinogenicity study, glyphosate (94.6–97.6% pure) was administered to groups of Sprague-Dawley rats in the diet. Groups of 50 rats/sex/group received diets containing 0, 3000, 10000, or 30000 ppm glyphosate for 24 months. The achieved doses were 0, 104, 354 or 1127 mg/kg/day in males and 0, 115, 393, or 1247 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose 10,000 ppm (1127 mg/kg/day in males and 1247 mg/kg/day in females) exceed the limit dose (1000 mg/kg/day) and there were increased cecum weights, distension of the cecum, loose stool, follicular hyperkeratosis and/or folliculitis/follicular abscess of the skin, and decreased body weights.

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7. **Nufarm. (2009a). Glyphosate Technical: Dietary Combined Chronic Toxicity/ Carcinogenicity in the Rat. Shardlow, Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015)**.

a. Experimental Design

In a combined chronic toxicity study, glyphosate (95.7% pure) was administered to groups of Wistar rats in the diet. Groups of 51 rats/sex/group received diets containing 0, 1500, 5000, and 15,000 ppm glyphosate for 24 months. To ensure that a received limit dose of 1000 mg/kg/day was achieved, the highest dose level was progressively increased to 24000 ppm. The achieved doses were 0, 86, 285 or 1077 mg/kg/day in males and 0, 105, 349 or 1382 mg/kg/day, in females. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were seen in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details are provide by Greim *et al.,* 2015 can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in either sex at any dose level.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest doses 1077 mg/kg/day in males and 1382 mg/kg/day in females exceed the limit dose (1000 mg/kg/day).

B. Carcinogenicity Studies in Mice

1. Knezevich, A.L and Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamic Inc., dated July 21, 1983. Report No. 77-2011. EPA Accession No. 251007 – 251009, and 251014.

a. Experimental Design

In a carcinogenicity study, groups of 50 male and female CD-1 mice received glyphosate (99.78%, pure) at dietary levels of 0, 1000, 5000, or 30,000 ppm for two years. These doses were equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, and histopathological examination.

b. Discussion of Tumor Data

The incidences of renal tubule adenomas were as follows: 0/49 in the controls; 0/49 at the low-dose; 1/50 at the mid-dose; and 3/50 at the high dose (TXR No. 0004370).

In 1985, the Registrant directed a re-evaluation of the original renal section by a consulting pathologist (Dr. Marvin Kuschner). This evaluation identified a small renal tubule adenoma in one control male mouse (animal number 1028) which was not diagnosed as such in the original pathology report (TXR No. 0004855).

In 1986, at the request of the agency, additional renal sections (3 sections/kidney/mouse spaced at 150 micron intervals) were evaluated in all control and all glyphosate-treated male mice in order to determine if additional tumors were present. The additional pathological and statistical evaluations concluded that the renal tumors in male mice were not compound-related (TXR No. 0005590).

At the request of the agency, the Pathology Work Group (PWG) examined all sections of the kidneys including the additional renal sections. The renal tubular-cell lesions diagnosed by the PWG are presented below in Table 13. The PWG noted that because differentiation between tubular-cell adenoma and tubular-cell carcinoma is not always clearly apparent and because both lesions are derived from the same cell type, it appropriate to combine the incidences for purposes of evaluation of statistical analysis. Statistical analyses are presented in Table 14. The PWG unanimously concluded that these lesions are not compound-related based on the following considerations: 1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the controls and there was no evidence of a significant linear trend; 3) multiple renal tumors were not found in any animal; and 4) compound-related nephrotoxic lesions,

including pre-neoplastic changes, were not present in male mice in this study (TXR No. 0005590).

Table 13. Glyphosate: Kidney Tumor in Male CD-1 Mice — PWG				
Dose/Tumor Type	Control	1000 ppm	5000 ppm	30,000 ppm
	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Tubular-cell adenoma	1/49	0/50	0/50	1/50
Tubular-cell carcinoma	0	0/50	1/50	2/50
Combined incidence	1/49 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)

Statistical analysis of the male mouse renal tumors diagnosed by the PWG are presented below in Table 14.

Table 14. Kidney Tumors in Male CD-1 Mice — PWG Cochran-Armitage Trend & Fisher's Exact Test (MRID 00130406)				
Tumor Type	0 mg/kg/day	161 mg/kg/day	835 mg/kg/day	4945 mg/kg/day
Adenomas (%) P =	1/49 (2) 0.4422	0/49 (0) 1.0000	0/50 (0) 1.00000	1/45 (2) 0.7576
Carcinomas (%) P =	0/49 (0) 0.0635	0/49 (0) 1.0000	1/50 (2) 0.5051	2/50 (4) 0.2525
Combined (%) P =	1/49 (2) 0.0648	0/49 (0) 1.0000	1/50 (2) 0.7576	3/50 (6) 0.3163

Historical control data from the testing laboratory (Bio-dynamics) during the glyphosate-study period (1976-1982) are presented in Table 15.

Table 15. Historical Control Data- Kidney tumors in CD-1 Mice — Bi/dynamics Inc.														
Study I.D	A		B		C		D		E		F		G	
Study Period	6/78 - 7/80		12/77- 4/80		12/77- 3/80		10/78- 4/81		11/78- 4/81		11/77- 4/80		10/77-4/80	
No. Examined	57	54	61	51	53	59	60	60	60	60	60	60	60	60
Tubular Adenoma		1	0	0	0	0	0	0	0	2	0	0	0	0

Historical control data from 14 studies conducted between 1977 and 1981 at the testing laboratory indicated that the mouse renal tumors ranged from 0 to 3.3% and the incidence in the current study (3/50; 6%) exceeded the upper limit of the historical control range (TXR No. 0007252).

The CPRC determined that glyphosate produced an equivocal carcinogenic response in male mice characterized by an increased incidence of renal tubular neoplasms. The biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls for adenomas, carcinomas and the combined tumors; b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (*e.g.* tubular necrosis/regeneration, hyperplasia, hypertrophy, etc.), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males; e) although the incidences exceeded the historical control, this finding did not override the lack of statistical significance of comparison to the concurrent controls. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not consider the renal tumors to be treatment-related. The CARC reaffirmed the CPRC conclusion and rationale. Also, the lack of increased renal tumors in the other mouse studies in the same strain provides additional evidence for lack of an actual carcinogenic response in the kidneys.

c. Non-Neoplastic Lesions

The incidence of centrilobular hepatocyte hypertrophy was slightly but not significantly increased in high-dose male mice at terminal sacrifice if all mice were included in the analyses. Centrilobular hepatocyte necrosis was significantly ($P \leq 0.01$) increased in high-dose male mice (10/50; 20%) compared to controls (2/49; 4%). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice. There was a dose-dependent increase in the proximal tubular epithelial basophilia in female mice; the incidences were: 0/50 (0%) in the controls, 2/50 (4%) at the low dose, 4/50 (8%) at the mid dose, and 9/50 (18%) at the high dose ($P \leq 0.01$). All other tissue alterations occurred sporadically and were found with approximately equal frequency and severity in control and treated animals. These were considered unrelated to glyphosate treatment.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The high dose tested in males (4945 mg/kg/day) and females (6069 mg/kg/day) was approximately 4 to 6-fold higher than the limit dose (1000 mg/kg/day), which produced highly significant reduction in body weights in both sexes. Therefore, the doses tested were determined to be adequate to assess the carcinogenic potential of glyphosate in this study.

2. Atkinson, C., Martin, T., Hudson, P., and Robb, D. (1993). Glyphosate: 104 week dietary carcinogenicity study in mice. Inveresk Research International, Tranent, EH33 2NE, Scotland. IRI Project No. 438618. April 7, 1993. MRID 49631702.

a. Experimental Design

In a carcinogenicity study, glyphosate (97.5 – 100.2% pure) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. No interim sacrifices were performed. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, necropsy and histopathological examination.

b. Discussion of Tumor Data

As shown in Table 16, hemangiosarcomas were found in 4/45 (9%) high-dose male mice compared to none in the controls. In the treated mice at the high dose, one had the tumors present in the liver and spleen, one had the tumor present in the liver only, one had the tumors present in the liver, spleen, and prostate, and one had the tumor present in the spleen only. No hemangiosarcomas were found in the control or low- and mid-dose mice.

Table 16. Hemangiosarcomas in Male CD-1 Mice Fisher's Exact Test and Exact Trend Test Results

Dose (mg/kg/day)	0	100	300	1000
Hemangiosarcomas	0/47[a]	0/46	0/50	4/45
(%)	(0)	(0)	(0)	(9)
P =	0.00296**	1.00000	1.00000	0.05332

a= Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in hemangiosarcomas in male mice was not considered to be treatment-related due to 1) tumors seen only at the limit dose; 2) absence of statistical significance in the pairwise analysis; 3) the incidences was near or the same as the upper limit (0–8%) for the performing laboratory; 4) hemangiosarcomas were not seen in male mice in the other three studies when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4348–5874 mg/kg/day) in this strain of mouse; 6) the considerable inter-group variability in the number of female mice with this tumor (0, 2 , 0 and 1 in the control, low-, mid- and high-dose groups, respectively); 7) Hemangiosarcomas are commonly observed in mice as both spontaneous and treatment-related tumors arising from endothelial cells; 8) hemangiosarcomas appear in both sexes but are generally more common in males (CD-1); 9) As vascular tumors, they can occur at different sites but liver and spleen tend to be the most common sites in male mice.

c. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose tested was the limit dose (1000 mg/kg/day).

3. **Arysta Life Sciences. (1997b). HR-001: 18-Month Oncogenicity Study in Mice. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology (Cited in Greim *et al.*, 2015)**.

a. Experimental Design

In a carcinogenicity study, groups of ICR-CD-1 mice (50/sex/group received diets containing glyphosate (94.6–97.6% pure) at 0, 1600, 8000 or 40,000 ppm for 18 months. The achieved doses were 0, 165, 838 or 4348 mg/kg/day in males and 0, 153, 787 or 4116 mg/kg/day in females, respectively. Parameters evaluated included clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, organ weights, gross necropsy and histopathological examination.

b. Survival Analysis

No adverse effects on survival were observed in either sex across the doses tested.

c. Discussion of Tumor Data

There were no statistically significant increases in any tumor type in this study. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

d. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

e. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested in both sexes exceeded (4-fold) the limit dose (1000 mg/kg/day).

4. Nufarm. (2009b). Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Derbyshire, UK: Harlan Laboratories Ltd. (Cited in Greim *et al.*, 2015).

a. Experimental Design

In another feeding study, CD-1 mice (50/sex/dose) received glyphosate (94.6–97.6%, pure) at 0, 500, 1500, or 5000 ppm for 18 months. The calculated test substance intake was 0, 85, 267 or 946 mg/kg/day. Parameters evaluated included clinical signs, body weight, food consumption, organ weights, gross necropsy and histopathological examination.

b. Discussion of Tumor Data

In male mice at the high dose (5000 ppm) there were increases in the incidences of adenocarcinomas of the lung and malignant lymphomas as shown in Tables 17. For the lung adenocarcinomas, the increases did not reach statistically significant pairwise differences, although the trend was significant. For the malignant lymphomas there was a trend and pairwise significance. Details provided by Greim *et al.* (2015) can be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423

Table 17. Lung Adenocarcinomas and Malignant Lymphomas in Male CD-1 Mice (Greim *et al.*, 2015)
Fisher's Exact Test and Exact Trend Test Results

Dose (ppm)	0	500	1500	5000
Lung Adenocarcinoma	5/51[a]	5/51	7/51	11/51
(%)	(10)	(10)	(14)	(22)
P =	0.02906**	0.62953	0.37996	0.08609
Malignant Lymphoma	0/51	1/51	2/51	5/51
(%)	(0)	(2)	(4)	(10)
P =	0.006633**	0.50000	0.24752	0.02820*

a= Number of tumor bearing animals/Number of animals examined.
Note: ** Significance of trend (P<0.01) denoted at control.

The increase in lung adenocarcinomas was not considered to be treatment-related due to: 1) absence of statistical significance in the pairwise analysis; 2) the incidences in all treatment groups including the controls were within the historical control range (1.43–26%) for the performing laboratory; and 3) lung tumors were not seen in the other three studies when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

Historical control data and results from the 5 studies can be used to put this finding into perspective. The malignant lymphomas were not considered to be treatment-related since the 0% incidence of this lesion in the concurrent control for male mice was lower than the historical control mean (4.5%) and range (1.5–21.7%) in this strain and age of mice (Gikins and Clifford, 2005; Son and Gopinath, 2004). Therefore, the apparent statistical significance of the pairwise comparisons of the high dose male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response. In addition, malignant lymphomas were not seen in the other three studies in this strain of mice when tested at doses ranging from 814 to 4945 mg/kg/day for up to two years.

c. Non-Neoplastic Lesions

There were no treatment-related non-neoplastic lesions in this study.

d. Adequacy of the Dosing for Assessment of Carcinogenicity

The highest dose (947 mg/kg/day) tested approached the limit dose (1000 mg/kg/day).

IV. TOXICOLOGY

A. Metabolism

Single or repeated doses of radiolabeled ^{14}C-glyphosate were administered orally to male and female Sprague-Dawley rats. Following a single oral dose of, ^{14}C-glyphosate, 30 to 36% of the dose was absorbed and less than 0.27% of the dose was eliminated as CO_2. 97.5% of the administered dose was excreted in the urine and feces as the parent compound, glyphosate. Amino methyl phosphonic acid (AMPA) was the only metabolite found in urine (0.2–0.3% of the administered dose) and feces (0.2–0.4% of the administered dose). Less than 1.0% of the absorbed dose remained in tissues and organs, primarily in bone tissue. Repeated dosing at 10 mg/kg did not significantly change the metabolism, distribution or excretion of glyphosate.

In a second study, male and female Sprague-Dawley rats received single intraperitoneal injections of radiolabeled ^{14}C-glyphosate at 1150 mg/kg. Blood samples were collected 0.25, 0.50, 1, 2, 4, 6 and 10 hours after injection. Femoral bone marrow samples were collected from one third of the male and female rats sacrificed at 0.5, 4, or 10 hours after injection. Thirty minutes after injection of glyphosate, the concentration of radioactivity in the bone marrow of male and female rats was equivalent to 0.0044% and 0.0072%, respectively, of the administered dose. Assuming first order kinetics, the decrease in radioactivity in bone marrow occurred with a half-life of 7.6 and 4.2 hours for males and females, respectively. Similarly, the half-lives of the radioactivity in plasma were approximately 1 hour for both sexes. These findings indicate that very little glyphosate reaches bone marrow, that it is rapidly eliminated from bone marrow, and that it is even more rapidly eliminated from plasma.

B. Mutagenicity

In 1991, the Carcinogenicity Peer Review Committee concluded that there was no evidence of genotoxicity for glyphosate based on negative findings in submitted guideline studies for the bacterial reverse mutation test (MRID 00078620), *in vitro* mammalian cell gene mutation test in CHO cells (MRID 00132681), *in vivo* mammalian bone marrow chromosomal aberration test (MRID 00132683) and a "rec assay" used to detect DNA-damaging agents in *Bacillus subtilis* (MRID 00078619) (TXR 0008898).

Glyphosate has also been evaluated for its genotoxic potential in other regulatory and published literature studies. Extensive reviews of the available genotoxicity studies for glyphosate and glyphosate products were conducted by Williams *et al.* (2000) and by Kier and Kirkland (2013). IARC also conducted a review of the publically available genetic toxicity data for glyphosate and glyphosate-based formulations (IARC, 2015).

Williams *et al.*, (2000) concluded that "glyphosate is neither mutagenic nor clastogenic." Similarly, Kier and Kirkland (2013) concluded a "lack of genotoxic potential for both glyphosate and glyphosate based formulations (GBFs) in core gene mutation and chromosomal effect endpoints." Kier and Kirkland (2013) also stated that "the observations of DNA-damage effects seems likely to be secondary to cytotoxic effects." However, IARC (2015) concluded that "there is strong evidence that glyphosate causes genotoxicity." It should be noted that the IARC's conclusion was based not only on studies conducted with the active ingredient but also on studies conducted with the formulation products such as Roundup. Roundup is a combination of the active ingredient and other chemicals, including a surfactant (polyoxyethyleneamine) which enhances the spreading of spray droplets when contact foliage. Of note, the review article by Kier and Kirkland (2013) and supplemental information provided on the publisher's website were not considered in the IARC evaluation.

In this assessment, the CARC considered a total of 54 studies including those submitted to the agency under 40 CFR Part 158 as well as the studies presented in the review articles by Williams *et al.* (2000), Kier and Kirkland (2013), and the IARC monograph (2015). Consistent with OPP's Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment (http://www.epa.gov/pesticides/science/lit-studies.pdf), literature studies discussed in the reviews such as IARC that did not meet the Klimisch criteria for reliability (*e.g.* lack of adequate glyphosate purity information for the test material) were not considered by the CARC. The CARC determined the mutagenic potential of glyphosate in humans by conducting a weight-of-evidence evaluation of the results from the cited bacterial reversion (Ames) assays, *in vitro* mammalian gene mutation assays, *in vitro* and *in vivo* chromosomal aberration and micronucleus assays as well as other relevant assays evaluating DNA damage.

1. Bacterial reverse mutation assays

As shown in Table 18, glyphosate was not mutagenic in any of the *in vitro* bacterial mutation assays using *S. typhimurium* or *E. coli* tester strains with or without microsomal S9 metabolic activation. These results are consistent with the negative findings in the previously reviewed EPA guideline (870.5100) bacterial reverse gene mutation study (MRID 00078620).

Table 18. Results from Bacterial Reverse Gene Mutation Assays[1]

Author	Cell/Strain[2]	Purity	Highest test concentration	Results –S9	Results +S9
Akanuma,M. (1995)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.7%[3]	5000 µg/plate	Negative	Negative
Callander, R.D. (1996)	TA98, TA100, TA1535, TA1537; WP2P and WP2*uvr*A	95.6%[3]	5000 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	76.1%[4]	100 µg/plate	Negative	Negative
Flügge, C. (2010)	TA98, TA100, TA102, TA1535, TA1537	96.4%	3160 µg/plate	Negative	Negative
Flügge, C. (2009)	TA98, TA100, TA102, TA1535, TA1537	98.8%	3160 µg/plate	Negative	Negative
Jensen, J.C. (1991)	TA98, TA100, TA1535, TA1537	98.6%	2500 µg /plate w/o S9; 5000 µg /plate w/ S9	Negative	Negative
Li and Long (1988)	TA98, TA100, TA1535, TA1537, TA1538;	98%	5000 µg/plate	Negative	Negative
NTP (1992)	TA97, TA100, TA1535	98%	10,000 µg /plate	Negative	Negative
Schreib, G. (2010)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96%	5000 µg/plate	Negative	Negative
Shirasu et al. (1978)	TA98, TA100, TA1535, TA1537, TA1538 and WP2*uvr*A	98.4%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007c)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.0%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007a)	TA98, TA100, TA1535, TA1537; WP2uvrA	95.1%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009b)	TA98, TA100, TA1535, TA1537;WP2P and WP2*uvr*A	96.3%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2009a)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	96.66%	5000 µg/plate	Negative	Negative
Sokolowski, A. (2007b)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	97.7%	5000 µg/plate	Negative	Negative
Suresh, T.P. (1993)	TA98, TA100, TA1535, TA1537, TA1538	96.0%	1000 µg/plate	Negative	Negative
Thompson, P.W. (1996)	TA98, TA100, TA1535, TA1537; WP2*uvr*A	95.3%	5000 µg/plate	Negative	Negative

1. Studies cited in Williams *et al*. (2000), Kier and Kirkland (2013), or IARC monograph.
2. *S. typhimurium* strains (TA97, TA98, TA100, TA102, TA1535, TA1537, and/or TA1538) or *E. coli* strains (WP2P and WP2*uvr*A)
3. Glyphosate acid
4. Monoammonium glyphosate salt

2. *In vitro* mammalian cell gene mutation assays

Glyphosate did not induce forward mutations in mouse lymphomas cells or Chinese hamster ovary (CHO) cells in the presence or absence of metabolic (S9) activation (Table 19).

Table 19. Results from mammalian gene mutation assays[1].

Author	Assay Type	Cell type	Purity	Highest conc.	Result -S9	Result +S9
Clay (1996)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	95.6%	1.0 mg/mL	Negative	Negative
Jensen, J.C. (1991)	*In vitro* mammalian gene mutation	L5178Y mouse lymphoma cells/ tk locus	98.6%	5.0 mg/mL	Negative	Negative
Li and Long (1988)	*In vitro* mammalian gene mutation	CHO cells/ HGPRT locus	98%	22.5 mg/mL	Negative	Negative

1. Studies cited in Williams's *et al.* (2000), Kier and Kirkland (2013), or IARC monograph.

3. *In vitro* chromosomal aberration assays

Lioi *et al.* (1998a, 1998b) reported positive findings for chromosomal aberrations in human and bovine lymphocytes treated with glyphosate *in vitro* in the absence of S9 activity. As discussed in the Williams review, there is less confidence in the Lioi *et al.* results based on the use of an unusual 72-hour treatment protocol and the observation of reduced cell growth in glyphosate-exposed cells (an indication of a toxic effect) which can affect the evaluation of the study. Lioi *et al.* also reported chromosomal damage in lymphocytes treated with other known non-genotoxic pesticides in this study at concentration ranges similar to where they reported effects for glyphosate. By contrast, when the tests were performed according to the OECD guideline, Van de Waart (1995) reported no significant increase in chromosomal aberrations in human lymphocytes treated with up to 0.56 mg/mL (-S9) and 0.33 mg/mL (+S9) glyphosate, which are concentrations 3 orders of magnitude higher than those at which Lioi *et al.* reported aberrations. Glyphosate was negative in two other *in vitro* chromosomal aberrations studies using human lymphocytes (Fox, 1998; Manas *et al.* 2009) and did not induce chromosomal aberrations in Chinese hamster lung cells (Matsumoto, 1995; Wright, 1996). A summary of the findings is presented in Table 20.

Table 20. Results from *in vitro* chromosomal aberration assays[1].

Authors	Assay	Cell type	Purity	Highest test concentration	Result -S9	Result +S9
Van de Waart (1995)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	0.56 mg/mL with S9; 0.33 mg/mL w/o S9	Negative	Negative
Fox, V. (1998)	Chromosome Aberration	Human peripheral lymphocytes	95.6%[2]	1250 ug/mL	Negative	Negative
Lioi et al. (1998a)	Chromosomal Aberration	Human peripheral lymphocytes	>98%	1.4 mg/L	Positive	Not Tested
Manas et al. (2009)	Chromosomal Aberration	Human peripheral lymphocytes	96%	6 mM	Negative	Not Tested
Lioi et al. (1998b)	Chromosomal Aberration	Bovine peripheral lymphocytes	>98%	2.9 mg/L	Positive	Not Tested
Matsumoto, K. (1995)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.68%[2]	1000 ug/mL	Negative	Negative
Wright, N.P. (1996)	Chromosomal Aberration	Chinese Hamster Lung (CHL) cells	95.3%	1250 ug/mL	Negative	Negative

1. Studies cited in Williams *et al*., (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

4. *In vivo* micronucleus and chromosomal aberration assays

Numerous studies were evaluated to determine the potential for glyphosate to induce micronuclei in rodent bone marrow cells. Studies included both intraperitoneal (IP) and oral routes of glyphosate administration. In a literature study by Bolognesi *et al.* (1997), the authors reported an induction of micronuclei in male mice treated with up to 300 mg/kg (injected as two ½ doses). It is noted that this study included only 3 animals/dose, rather than the 5 animals/dose recommended in the agency's test guideline (870.5395). In another literature study, Manas *et al.* (2009) reported an induction of micronuclei in BALB/C mice when tested up to 200 mg/kg glyphosate. However, there is some concern regarding how the micronuclei were scored in this study. As stated in the Kier and Kirkland review, Manas *et al.* (2009) reported their findings as an increase in micronucleated erythrocytes rather than polychromatic erythrocytes. Scoring all erythrocytes rather than immature polychromatic erythrocytes can impact the interpretation of the study as the effects cannot be solely attributed to treatment by the test article. Suresh *et al.* (1993) reported an increase in micronuclei in females only in Swiss albino mice treated with 5 mg/kg glyphosate; however, this occurred at a dose that is more than twice the limit dose for the agency's guideline study. Although the above authors reported positive findings, a vast majority of the *in vivo* genotoxicity studies (including the previously reviewed guideline mammalian bone marrow chromosomal aberration test) were negative at doses similar to or higher than the studies discussed above, regardless of the dosing regimen or route of administration. Furthermore, glyphosate was also negative in two rodent dominant lethal tests. A summary of the findings are reported in Table 21.

Table 21. Results from *in vivo* genotoxicity assays[1].

Author	Assay Type	Species/strain	Purity	Highest conc.	Results	Comments
Bolognesi *et al.* (1997)	Micronucleus test	Male mice (strain not provided)	99.9%	300 mg/kg	Positive	Two IP injections of ½ dose; 3 mice/dose
Durward, R. (2006)	Micronucleus test	Young adult male and female albino Crl:CD-1TM(ICR)BR mice	95.7%	600 mg/kg	Negative	Single IP injection; Significant increase in % PCEs per 1000 erythrocytes was observed in the 24-hour; however not 48-hour at 600 mg/kg
Flügge, C. (2009)	Micronucleus test	Male and female CD rats	98.8%	2000 mg/kg	Negative	Single dose; oral gavage
Fox and Mackay (1996)	Micronucleus test	Male and female CD-1 BR mice	95.6%[2]	5000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2005)	Micronucleus test	Male and female NMRI mice	97.73%	2000 mg/kg	Negative	Single dose; oral gavage
Honavar, N. (2008)	Micronucleus test	NMRI male mice	99.1%	2000 mg/kg	Negative	Single dose; oral gavage
Jensen, J.C. (1991)	Micronucleus test	Young adult male and female NMRI SPF mice	98.6%	5000 mg/kg	Negative	Single dose; oral gavage
Manas *et al.* (2009)	Micronucleus	BALB/C mice	96%	200 mg/kg	Positive	Two IP doses, 1 day apart
NTP (1992)	Micronucleus test	Male and female B6C3F1 mice	99%	11,379 mg/kg/day	Negative	Dietary admin., 13 weeks
Suresh, T.P. (1993)	Micronucleus test	Young Swiss albino male and female mice	98.6%	5000 mg/kg	Males: Negative Females: Positive	Two doses 1 day apart; oral gavage
Suresh, T.P. (1994)	Mouse Bone Marrow Chromosome Aberration	Male and female Swiss albino mice	96.8%	5000 mg/kg	Negative	Two doses, 24 hours apart; oral gavage
Suresh, T.P. (1992)	Rodent dominant lethal test	Male and female Wistar rats	96.8%	500 mg/kg (single dose); 100 mg/kg (5 daily doses)	Negative	
Wrenn (1980)	Rodent dominant lethal test	Mouse; gavage	98.7%	2000 mg/kg	Negative	

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid
3. IP= intraperitoneal injection

5. Other genotoxicity assays

Inconsistent responses were reported in a number of assays designed to detect DNA damage, including sister chromatid exchange (SCE) assay, unscheduled DNA synthesis assay, and the comet assay (also known as the single cell electrophoresis assay). Positive responses in these assays do not necessarily indicate a chemical is DNA-reactive (*i.e.* mutagenic), but rather that DNA damage occurred under conditions of the assay. Glyphosate was also negative in two Rec-DNA repair tests in *B. subtilis*. The results of these genotoxicity studies are presented in Table 22.

Table 22. Additional genotoxicity assays of glyphosate

Authors	Assay Type	Cell Type	Purity	Highest test conc.	Results
Bolognesi *et al.* (1997)	Sister chromatid exchange (SCE)	Human peripheral blood (*in vitro*)	99.9%	1000 ug/mL	Positive
Lioi *et al.* (1998a)	SCE	Human peripheral blood (*in vitro*)	>98%	1.4 mg/L	Equivocal
Lioi *et al.* (1998b)	SCE	Bovine peripheral blood (*in vitro*)	>98%	2.9 mg/L	Equivocal
Li and Long (1988)	Unscheduled DNA synthesis (UDS)	Rat hepatocytes (*in vitro* exposure)	98%	0.125 mg/mL	Negative
Rossberger,(1994)	UDS	Primary rat hepatocytes	98%	111.69 mM	Negative
Bolognesi *et al.* (1997)	DNA Damage /reactivity/UDS	Mouse; IP administration	99.9%	300 mg/kg	Equivocal
Bolognesi *et al.* (1997)	DNA Damage/reactivity/UDS	Mouse; IP; alkaline solution of extracted DNA	99.9%	300 mg/kg	Positive
Alvarez-Moya et al. (2014)	Comet assay	Human lymphocytes	96%[2]	700 µM	Positive
Lueken *et al.* (2004)	Comet assay	Human fibroblasts GM 5757	98.4%	75 mM	Negative
Manas *et al.*(2009)	Comet assay	Liver Hep-2 cells	96%	7.5 mM	Positive
Mladinic et al. (2009)	Comet assay	Human lymphocytes	98%	580 ug/mL (toxic); approximately 3.43 mM	Positive
Rossberger, S. (1994)	DNA repair test	Male SD rat primary hepatocytes	>98%	111.69 mM	Negative
Akanuma, M. (1995)	DNA repair test (Rec- assay)	*Bacillus subtilis* M45 rec-/ H17 rec+	95.68%[2]	240 ug/disk	Negative
Li and Long (1988)	DNA repair test (Rec assay)	*B. subtilis* H17, rec+; M45, rec-	98%	2 mg/disk	Negative

1. Studies cited in Williams *et al.*, (2000), Kier and Kirkland (2013), or IARC monograph.
2. Glyphosate acid

6. Conclusions

In summary, glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronuclei or chromosomal aberration studies considered in this assessment by the CARC. Some positive results were reported in SCE and comet assays in the open literature; however, there is no convincing evidence that the DNA damage is a direct effect of glyphosate exposure, but rather may be secondary to cytotoxicity or oxidative damage.

C. Structure-Activity Relationship

At present there are no structurally related pesticides registered by the agency which resemble glyphosate. Sulfosate, the trimethylsulfonium salt of glyphosate (also known as glyphosate-trimesium) is a 1:1 molar salt of N-(phosphonomethyl) glycine anion (PMG) and the trimethylsulfonium cation (TMS). Sulfosate was evaluated for its carcinogenic potential following dietary administration to male and female mice at 0, 10, 1000 or 8000 ppm (equivalent to 0, 16, 159 or 1341 mg/kg/day, respectively) for 18 months, and in male and female Sprague-Dawley rats at 0, 100, 500, or 1000 ppm (equivalent to 0, 5.4, 27 or 557 mg/kg/day, respectively) for two years. There was no evidence of carcinogenicity in either species. Sulfosate is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans" based on the absence of carcinogenicity in mice and rats in two acceptable studies. Based on the available mutagenicity studies, there is no concern for mutagenicity (TXR Nos. 0006452 and 0011156).

D. Subchronic and Chronic Toxicity Studies

1. Subchronic Toxicity

In a 90-day feeding study (MRID No. 00036803) CD-1 mice were fed diets containing 0, 250, 500 or 2500 mg/kg/day of glyphosate for three months. Body weight gains of the high-dose males and females were about 24% and 18% lower, respectively, than those of the controls. Body weight gains of the low-dose and mid-dose groups were comparable to those of the controls. For systemic toxicity, the NOAEL is 500 mg/kg/day and the LOAEL is 2500 mg/kg/day, based on decreased body weight gain in both sexes.

In a 90-day feeding study (MRID No. 40559401), Sprague-Dawley rats were fed diets containing 0, 63, 317, and 1267 mg/kg/day of glyphosate, respectively in males and 0, 84, 404 and 1623 mg/kg/day of glyphosate, respectively, in females. Treatment-related findings were: (1) increased serum phosphorus and potassium in all treated groups, males and females; (2) increased serum glucose in the mid-dose and high-dose males; (3) increased blood urea nitrogen (BUN) and serum alkaline phosphatase in the high-dose males; and (4) occurrence of pancreatic lesions in the high-dose males (pancreas was not examined at the low-dose and mid-dose groups). Based on these findings, the systemic NOAEL is <1000 ppm (not determined definitively) for both sexes.

2. Chronic Toxicity

(i) Rats

A chronic feeding/carcinogenicity study (MRID No. 00093879) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 30, 100, or 300 ppm of glyphosate for 26 months. These levels were equivalent to 0, 3, 10, and 34 mg of glyphosate/kg/day, respectively. There were no effects based on any of the parameters examined (toxic signs, mortality, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights and organ/tissue pathology). Therefore, the NOAEL for systemic toxicity is 300 ppm (males: 31 mg/kg/day and females: 34 mg/kg/day).

A second chronic feeding/carcinogenicity study (MRID No. 41643801) was conducted using male and female Sprague-Dawley rats which were fed diets containing 0, 2000, 8000, or 20,000 ppm of glyphosate for two years. These levels were equivalent to 0, 89, 362, or 940 mg/kg/day, respectively, for the males and 0, 113, 457, or 1183 mg/kg/day, respectively, for the females. Treatment-related effects observed only in the high-dose group included: (1) decreased body weight gain in females; and (2) increased incidence of cataracts and lens abnormalities, decreased urinary pH, increased absolute liver weight, and increased liver weight/brain weight ratio (relative liver weight) in males. No significant systemic effects were observed in the low-dose and mid-dose male and female groups. Therefore, the NOAEL for systemic toxicity is 8000 ppm (males: 362 mg/kg/day and females: 457 mg/kg/day) and the LOAEL is 20,000.

In a combined chronic toxicity/carcinogenicity study (MRID No. 49631701), glyphosate (98.9% a.i.) was administered to 85 Sprague-Dawley rats/sex/dose in the diet for 104 weeks ater 0, 10, 100, 300, and 1000 mg/kg/day to both sexes over the course on the study. Designated for the toxicity portion of the study were 35 rats/sex/dose with the remainder designated for the oncogenicity portion of the study. There were no statistical differences between treated and control groups in survival rates. Pale feces were observed during weeks 16–104 in both sexes at the high dose and in females from the low-mid and high-mid dose levels. No treatment-related effect was observed in food consumption, hematology, ophthalmology, and gross pathology data. Males from the high-dose group had statistically lower mean body weight ($P \leq 0.01$) by 5% to 11% beginning Week 2 of the study until Week 104, and at termination was 10% lower (-14% weight gain). Females at the high dose had statistically lower body weight ($P \leq 0.05$) by 5% to 12% beginning Week 20 through Week 80 (with several exceptions), and at termination was 8% lower (-11% weight gain). Statistically increased ALP activities (+46% to +72%) were observed in males at the high dose throughout the study except for the 51 week interval when the mean value was 31% higher than control. Elevated ALP activities were observed in females at the high dose (+34% to +53%) throughout the study, and through most of the study at the high-mid dose by +20% to +67%, though not always statistically significant. Urinalysis data showed reduced pH (5.5–6) in males at the high dose throughout the study.

The absolute liver weight was decreased significantly in females at the high dose after 52 weeks, but after correcting for final body weight the difference was statistically significant at the three highest doses. The parotid salivary gland weight was increased significantly in males at the three highest doses (56–111%) after 52 weeks, but not after 104 weeks. The combined weight of the sublingual and submaxillary salivary glands was significantly increased by 13% (22% after correcting for body weight) at the high dose after 52 weeks. In females, the parotid gland was not affected but the sublingual and submaxillary combined weight was significantly higher by about 15%. The changes in salivary gland weights were accompanied by increased incidence of mild to severe parotid salivary gland cell alterations and slight to moderate mandibular salivary gland cell alterations were observed in both sexes at the 52-week and 104-week intervals. The lesions were described as cells and/or acini that appeared larger and stained in a weakly basophilic manner without showing a tendency toward proliferative or degenerative changes over time. In males, the increased incidence and severity of lesions in the parotid gland were significant ($P \leq 0.01$) at 100, 300, and 1000 mg/kg bw/day at 52 weeks, and significant at 300 and 1000 mg/kg bw/day at 104 weeks. The increased incidence of lesions in the mandibular gland were significant at 300 and 1000 mg/kg bw/day at 52 weeks and significant ($P \leq 0.001$) at 100, 300, and 1000 mg/kg bw/day at 104 weeks. In females, the increased incidence of parotid lesions was significant at 300 and 1000 mg/kg bw/day at 52 weeks, and significant at 100, 300, and 1000 mg/kg bw/day at 104 weeks. The increased incidence in the mandibular gland lesions was significant at the high dose at both 52 and 104 weeks. The incidence and/or severity of kidney nephropathy decreased in males at 100, 300, and 1000 mg/kg bw/day at 52 weeks and at the high dose at 104 weeks. Urothelial hyperplasia significantly decreased in females from the high dose group at both the 52-week and 104-week intervals. The LOAEL in male and female Sprague-Dawley rats administered glyphosate for 104 weeks in the diet was 100 mg/kg bw/day based on microscopic lesions in the parotid and mandibular salivary glands. The NOAEL was 10 mg/kg bw/day (MRID No. 49631701).

In another chronic toxicity/carcinogenicity study (MRID No. 49704601), groups of 52 male and 52 female Alpk:APSD (Wistar-derived) rats were fed diets containing glyphosate at 0, 2000, 6000, or 20,000 ppm for two years. These doses were equivalent to 0, 121, 361 or 1214 mg/kg/day in males and 0, 145, 437, or 1498 mg/kg/day in females, respectively. Treatment-related findings were confined to the liver and kidneys at the highest dose (20,000 ppm). In both sexes, treatment-related changes manifested as papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, and hematuria. The LOAEL was 20,000 ppm (1214 mg/kg/day in males and 1498 mg/kg/day in females) and the NOAEL was 6000 ppm (361 mg/kg/day in males and 437 mg/kg/day in females)

(ii) Mice

In a carcinogenicity study (MRID No. 00251007), glyphosate (Technical, 99.7% a.i.) was administered to groups of 50 male and 50 female CD-1 mice/sex/dose in the diet at dose levels of 0, 1000, 5000, or 30,000 ppm (approximately equivalent to 0, 161, 835, 4945 mg/kg bw/day for males and 0, 195, 968, and 6069 mg/kg bw/day for females) for 24 months. Cage-side and detailed clinical observations were done. Body weight and food intake were monitored throughout the study. Water consumption was measured during months 12 and 24. Erythrocyte, as well as total

white cell counts and differentials, were done at months 12, 18, and 24. Tissues and organs were collected from all mice whether dying during the study or at terminal sacrifice. Microscopic analyses were done on all collected tissues.

No treatment-related effects were found on survival, body weight, food or water consumption, or hematology parameters of treated male or female mice. The terminal body weight of high-dose males was significantly decreased 9% while the absolute liver weight of high-dose males was significantly decreased 16%; however, no significant treatment-related effects were found on the liver-to-body-weight ratio. The absolute testes weight of high-dose male mice was increased 7%, while the relative to body testes weight was increased 17. Neither were statistically significant, and no microscopic histological correlates were found. The incidences of centrilobular hepatocyte hypertrophy were slightly, but not significantly increased in high-dose male mice. Centrilobular hepatocyte necrosis was significantly higher in high-dose males (10/50** (20%) vs. control 2/49 (4%), $P \leq 0.01$). No significant increases in centrilobular hepatocyte hypertrophy or necrosis were observed in treated female mice; however, proximal tubular epithelial basophilia was significantly increased in high-dose females (9/50 (18%) vs control 0/50 (0%), $P \leq 0.01$). No other microscopic treatment-related effects were found. Based on increased centrilobular hepatocellular necrosis in high-dose males and proximal tubular epithelial basophilia in high-dose females, the systemic LOAEL for male and female CD-1 mice was 30,000 ppm (approximately 4945 mg/kg bw/day for males and 6069 mg/kg bw/day for females). The NOAEL for the study was 835 mg/kg bw/day for males and 968 mg/kg bw/day for females) (MRID No. 00251007).

In another carcinogenicity study (MRID No. 49631702), glyphosate (97.5–100.2% a.i.) was administered to groups of 50 CD-1 mice/sex/dose in the diet at doses of 0, 100, 300, or 1000 mg/kg/day for 104 weeks. Mortality, body weight, body weight gain, and food consumption were monitored throughout the study. WBC differential counts were done during Weeks 52, 77, and 102 of the study. Organ weights were measured and tissues collected for microscopic analyses. Treatment of male and female mice for 104 weeks did not increase mortality and did not decrease body weight, body weight gain or food consumption. No treatment-related clinical signs of toxicity were observed and no effects were found on WBC differential counts. Treatment did increase the absolute and relative thymus weights of male and female mice treated with 300 or 1000 mg/kg bw/day approximately 2–3-fold, but only the results of male mice were statistically increased. However, no treatment-related effects were found microscopically. At necropsy, the incidence of lung masses was slightly increased in high-dose male mice, but were considered coincidental. Microscopically, there was a slight, but statistically significant increase in mineral deposition in the brains of mid- and high-dose male mice. A non-significant increase was observed in female mice. Kidney cysts were also slightly but statistically increased in low- and mid-dose males, but no increase of cortical tubular eosinophilic droplets was found in female mice. The significance of these findings is questionable since they did not follow a dose-response. The systemic NOAEL for glyphosate in male and female CD-1 mice treated up to 104 weeks was 1000 mg/kg bw/day. A LOAEL was not identified (MRID No. 49631702).

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

A. Evidence for Carcinogenicity in Humans

The CARC evaluated one cohort study and seven nested case-control studies based on the cohort study population and twenty-five case-control studies that examined the association between glyphosate exposure and one or more cancer outcomes.

1. Cancer at Multiple Sites

Several case-control studies reported no association for cancer of the oral cavity, colon, rectum, colorectum, lung, pancreas, kidney, bladder, prostate, breast or melanoma from exposure to glyphosate (De Roos *et al.*, 2005; Engle *et al.*, 2005; Lee *et al.*, 2007; Andreotti *et al.*, 2009; and Dennis *et al.*, 2010).

In single case-control studies, no associations were found for cancers of the esophagus, stomach, prostate or soft-tissue sarcoma from exposure to glyphosate (Alavanja *et al.*, 2003; Lee *et al.*, 2004; Band *et al.*, 2011; Pahwa, *et al.*, 2011; Koutros *et al.,* 2013). No association for childhood cancer was found from maternal or paternal exposure to glyphosate (Flower *et al.*, 2004).

2. Brain Cancer

A case-control study in Nebraska and the Upper Midwest Health case-control study in Iowa, Michigan, Minnesota and Wisconsin did not find any no association of glyphosate with adult brain cancer, specifically for gliomas (Ruder *et al.*, 2004; Carreon *et al.*, 2005; and Lee *et al.*, 2005).

3. Leukemia

No significant association with leukemia was reported in a case-control study in Iowa and Minnesota (Brown *et al.*, 1990) or in the AHS cohort (De Roos *et al.*, 2005). A Swedish case-control study reported a non-statistically significant elevated risk for hairy cell leukemia. However, the authors stipulated that this risk should be interpreted with caution since it was based on only 4 glyphosate-exposed cases (Nordstrom *et al.*, 1998).

4. Multiple Myeloma

No significant association for multiple myeloma from exposure to glyphosate was found in three separate population-based case-control studies: one in Iowa and Minnesota (Brown *et al.*, 1993) and the other in Iowa and North Carolina, USA (De Roos *et al.*, 2005; Sorhan 2015); and the third study in Canada (Pahwa *et al.*, 2012; Kachuri *et al.*, 2013), and in a hospital-based case-control study in France (Orsi *et al.*, 2009). A cohort study found no association with glyphosate exposure and monoclonal gammopathy of undetermined significance, a pre-clinical marker of multiple myeloma progression (Landgren *et al.*, 2009).

5. Non-Hodgkin Lymphoma

There is conflicting evidence for an association between glyphosate exposure and NHL; seven case-control studies reported no association in the U.S, Canada, and France, while two case-control studies from Sweden reported positive association.

No association between glyphosate exposure and NHL was found in four population-based case-control studies in the United States: in Iowa and Minnesota (Cantor *et al.*, 1992); in Iowa, Nebraska and Minnesota (Lee *et al.*, 2004a); in Iowa, Nebraska, Minnesota and Kansas (De Roos *et al.*, 2003) and in the AHS cohort with 57,311 licensed pesticide applicators in Iowa and North Carolina (De Roos *et al.*, 2005).

Similarly, no association between glyphosate exposure and NHL was seen in two population-based case-control studies conducted in various Canadian provinces (McDuffie *et al.*, 2001; Hohenadel *et al.,* 2011).

A hospital based case-control study from France did not find an association between glyphosate exposure and NHL (Orsi *et al.*, 2009).

The first report of an association between glyphosate exposure and NHL was in a population-based case-control study from Sweden (OR=23.3; 95% CI=0.40–13.0); however, this finding was based on only 4 glyphosate-exposed cases and 3 controls (Hardell and Erickson, 1999).

In a 2002 follow-up study, data from two case-control studies in Sweden, one on NHL and the other on hairy cell leukemia, were pooled and analyzed. A univariate analysis showed an increased risk (OR=3.04; 1.08–8.52); however, when study site, vital status, and exposure to other pesticides were taken into account in a multivariate analysis, risk declined (OR=1.85; 95% CI=0.55–6.20) (Hardell *et al.*, 2002).

In another case-control study in Sweden, among the 29 glyphosate-exposed cases, a multivariate analyses showed a statistically significantly increased risk for NHL (OR=1.51; 95% CI=0.77–2.94) and B-cell lymphoma (OR=1.87; 95% CI=0.998–3.51) (Erickson *et al.*, 2008).

A meta-analysis of the six studies (De Roos *et al.,* 2003; 2005; McDuffie *et al.*, 2001; Hardell *et al.*, 2002; Erickson *et al.*, 2008; and Orsi *et al.*, 2009) that showed an association between glyphosate exposure and NHL, resulted in a meta-risk ratio of 1.5 (95% CI=1.1–2.0) (Schinasi and Leon, 2014).

In an attempt to address the noted power/sample size issues and after considering the adjusted estimates of the two Swedish studies, IARC performed a meta-analysis of the data and estimated a meta-risk ratio of 1.3 (95% CI=1.03–1.65) (IARC, 2015).

In summary, the epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and non-solid tumors: leukemia, multiple myeloma or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate exposure and NHL. Multiple case-control studies and one prospective cohort study found no association with NHL; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Most of the studies in the database were underpowered, suffered from small sample size of cancer cases with glyphosate exposure, and risk/odds ratios with large confidence intervals. Additionally, some of the studies had biases associated with recall and missing data. The CARC recognizes the meta-analysis conducted by IARC to try to address the power/sample size issues. However, given the limitations of the studies used, a different weighting scheme could easily change the meta-risk ratio. Thus, while the epidemiologic literature to date does not support causal association, the CARC recommends that the literature continue to be monitored for studies related to glyphosate and risk of NHL.

B. Evidence for Carcinogenicity in Experimental Animals

1. Evidence for Carcinogenicity in Rats

A total of seven chronic toxicity/carcinogenicity studies in Wistar or Sprague-Dawley strain rats were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 3.0 mg/kg/day to 1500 mg/kg/day for 2-years.

(i) Testes

In Sprague-Dawley rats (MRID No. 00093879), there was a non-dose-related increase in the incidences of interstitial cell tumors in the testes of males at 3 mg/kg/day (6%), 10 mg/kg/day (2%) and 30 mg/kg/day (12%; P=0.013) when compared to controls (0%). The CARC reaffirmed the previous conclusion that these tumors are not treatment related based on the following considerations: 1) lack of dose-response; 2) absence of pre-neoplastic lesions (*i.e.*, interstitial cell hyperplasia); 3) the incidences were within the normal biological variation seen for this tumor type in this strain of rats; 4) the incidences in the concurrent controls (0%) was not representative of the normal background incidences noted in the historical control animals (mean, 4.5; range, 3.4% to 6.7%;) and 5) this finding is not replicated in the other studies in the same strain of rats (*i.e.*, no interstitial cell tumors were seen when tested up to 1100 mg/kg/day). The CARC concluded that the interstitial cell tumors are not treatment-related.

(ii) Pancreas

Benign pancreatic islet cell tumors were seen in male Sprague-Dawley rats in two studies. In the first study (MRID No. 00093879), there was no dose response or statistical significance; the incidences for adenomas were: 0%, 10%, 4% and 4% at the control, low, mid, and high dose groups. Carcinomas were seen in one rat at the high dose. In the second study (MRID No. 41643801), there was a statistically significant increase in adenomas at the lowest (100 mg/kg/day) and the highest (1000 mg/kg/day) doses compared to controls: lowest dose, 8/45 (18%; P=0.018); intermediate dose, 5/49 (10%); and highest dose, 7/48 (15%; P=0.042) versus controls, 1/43 (2%). The CARC reaffirmed the previous conclusion that the benign pancreatic islet cell tumors are not treatment-related due to lack of dose-response, absence of pre-neoplastic lesions, lack of progression to malignancy, and incidences within the historical control range (0–17%) reported for this tumor in this strain of rats. This neoplasm was not seen in the other five studies. The CARC concluded that the pancreatic islet tumors are not treatment-related.

(iii) Liver

In male Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of hepatocellular adenomas (P=0.016). The CARC concluded that the minimal increase in adenomas is not treatment-related due lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions, no progression to malignancy, and the incidences were within the historical control range (1.4–18.3%) of the testing laboratory.

In male Wistar rats (MRID No. 49704601), there was a statistically significant trend (P=0.00804) and pairwise significance for the increase in hepatocellular adenomas at the highest (1214 mg/kg/day) dose compared to controls: lowest dose, 2/52 (4%); intermediate dose, 0/52 (0%); and highest dose, 5/52 (10%; P=0.02826) versus controls, 0/52 (0%). The CARC concluded that this increase is not attributable to treatment based on the following considerations: 1) absence of dose-response relationship; 2) lack of progression to malignancy; 3) no evidence of pre-neoplastic lesions; 4) the incidences were within the historical control range (0–11.5%).

The CARC noted that survival was better at the high dose (25/52; 13%) compared to the controls (16/52; 8.3%) which could be reason for the slightly higher incidence (5/52) of age-related background tumors like liver adenomas in the absence of any associated lesions. Furthermore, with a weak genotoxic effect one would expect to see an effect on carcinomas (or at least adenomas/ carcinomas, combined) and shorter latency period, which were not observed in this study. With a weak cytotoxic or mitogenic effect one would expect to see an increase in foci and other non-neoplastic lesions. In addition, as discussed above, only a linear trend (no pairwise) was seen for this tumor type in another strain (Sprague-Dawley) for rats where the incidences were still within the historical control range. Also, liver tumors were not seen in the other four studies. This provides additional evidence for lack of an actual carcinogenic response in the liver. The CARC concluded that the liver tumors are not treatment-related.

(iv) Thyroid

In Sprague-Dawley rats (MRID No. 41643801), there was a statistically significant positive trend in the incidence of thyroid C-cell tumors in females (P=0.031). The CARC concluded that the minimal increase is not treatment-related due to lack of statistical significance in pairwise comparison, no progression to carcinomas, no increase in severity of grade or incidence of hyperplasia, and the incidences were within the historical control range (3.3–10%). The CARC concluded that the thyroid tumors in female rats are not treatment-related.

In summary, dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female Sprague-Dawley or Wistar rats.

2. Evidence for Carcinogenicity in Mice

Four carcinogenicity studies in CD-1 mice were available for review. In these studies, glyphosate was administered in the diet to both sexes at doses ranging from 85 mg/kg/day to 4800 mg/kg/day for 18–24 months. In one study there were no statistically significant or otherwise notable increases in the occurrence of any tumor types. Tumors observed in the other three studies are discussed below.

(i) Kidney

Kidney (renal tubular) tumors were seen in male CD-1 mice in one study (MRID No. 00251007). The incidences of adenomas was 1/49 (2%), 0/49 (0%), 0/50 (0%), and 1/50 (2%) in the control (0 mg/k/day), low- (157 mg/kg/day), mid- (814 mg/kg/day) and high-dose (4945 mg/kg/day) groups, respectively. The incidence of carcinomas was 0/49 (0%), 0/49 (0%), 1/50 (2%) and 2/50 (4%) in the control, low-, mid- and high-dose groups, respectively. The incidence of adenomas or carcinoma (combined) was 1/49 (2%), 0/50 (0%), 1/50 (2%), and 3/50 (6%) in the control, low-, mid-, and high-dose groups, respectively. None of these differences showed statistical significance.

The CARC reaffirmed the previous conclusion that the kidney tumors are not treatment-related based on the following weight-of-evidence considerations: a) lack of dose-related trend or statistical significance in pairwise comparisons; b) lack of non-neoplastic renal tubular lesions (*e.g.* tubular necrosis/regeneration, hyperplasia, or basophilia); c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well; and d) the difference in incidence between high-dose group (3/50) and the control group (1/49) was minimal, especially considering the very high concentration given (4 x time the limit dose).

Furthermore, the Pathology Work Group concluded that the renal tumors were not treatment-related since none of the treatment groups differed from the controls for a linear trend or pairwise statistical significance, there was no treatment-related nephrotoxic lesions including pre-neoplastic changes, and multiple renal tumors were not seen in any animal.

In addition, the CARC noted that renal tumors were not observed when tested at a similar dose (4348 mg/kg/day) in this strain of mice in another study(Arysta, 1997b) or in two other studies at the limit dose (MRID No. 49631702, Nufarm, 2009b). If really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000 – 4000 mg/kg/day.

(ii) Lung adenocarcinoma

There was a dose-dependent increase in the incidence of bronchiolar-alveolar adenocarcinoma of the lung in male CD-1 mice (Nufarm, 2009b). There was a positive trend (P=0.02906) in the incidence of lung adenocarcinomas: 5/51 (10%), 5/51 (10%), 7/51 (14%) and 11/51 (22%) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related due to lack of statistical significance in pairwise comparison, absence of pre-neoplastic lesions in the lung (*e.g.*, bronchiolar-alveolar hyperplasia), and incidences in all treated groups within the background range (1.42–26%) for this tumor in this strain and age of mice. Also, lung tumors were not seen when tested at a comparable dose (1000 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other three studies (MRID Nos. 00251007; 49631702; Arysta, 1997b).

(iii) Lymphoma/Lymphosarcomas

There was a dose-dependent and statistically significant increase in the incidence of malignant lymphomas in male mice (Nufarm, 2009b). The incidence was: 0/51 (0%; trend P=0.006633), 1/51 (2%), 2/51 (4%) and 5/51 (10%; P=0.02820) at the 0, 85, 267 or 946 mg/kg/day groups, respectively. The CARC determined that this increase is not treatment-related since the incidences in the concurrent controls (0%) were not representative of the normal background incidences noted in the historical controls (mean, 4.5%; range, 1.5% to 21.7%), and the apparent statistical significance of the pairwise comparison of the high dose group with the concurrent control might have been attributable to this factor rather than an actual carcinogenic response. Also, this neoplasm was not seen in other studies in this strain of mice. For example, in the study by Knezevich and Hogan 1983 (MRID No. 00251007), there was no significant difference in the incidence of lymphomas between control and high-dose groups (P=1.00 for males, P=0.12 for females). In the study by Atkinson *et al.* (1993) (MRID No. 496317), the incidence values in "lymphoreticular/ hematopoietic tissue" were not significantly different between control and high-dose groups (males: 4 in controls, 6 in high-dose group; females: 14 in controls, 13 in high-dose group). In the Arysta 1997 study (Greim *et al.*, 2015), the incidence of lymphoma in males was 2/50, 2/50, 0/51, 6/50 in the control, low, mid and high dose groups, respectively. There were no statistically significant pairwise differences observed in any of these studies.

(iv) Hemangioscarcomas

Hemangiosarcomas were seen in multiple organs including, liver, spleen, and prostate in males and liver and uterus in female CD-1 mice (MRID No. 49631702). There was a positive trend (P=0.00296) in the incidence of hemangiosarcomas in male mice: 0/47 (0%), 0/46 (0%), 0/50 (0%) and 4/45 (9%) at the 0, 100, 300 and 1000 mg/kg/day groups, respectively. The hemangiosarcomas were present in the liver, spleen or prostate in the high dose males. In females, this neoplasm was seen in one female at the low dose (uterus) and in one high dose (spleen). The CARC did not consider the hemangiosarcomas in males to be treatment-related based on the following considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed in mice as spontaneous tumors and are generally more common in males in CD-1 strain mice; 5) there was not a significant increase in hemangiosarcomas seen in the other three mouse studies; and 6) if really treatment-related, it is unlikely that the same tumor would not have been detected at higher incidences in CD-1 mice with top doses >1000-4000 mg/kg/day.

In summary, dietary administration of glyphosate at doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in male or female CD-1 mice.

C. Discussion

When determining the carcinogenic potential of chemicals, the IARC identifies a cancer "hazard" if an agent (*e.g.*, chemical) is capable of causing cancer under some circumstance and the agent is termed "carcinogenic" if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The IARC also considers that there is "*sufficient evidence of carcinogenicity"* based on the occurrence of increased tumors (benign, malignant, or combination) in: 1) two or more species of animals; 2) two or more independent studies in one species; and/or 3) an increased incidence of tumors in both sexes of a single species. Furthermore, a single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites (IARC Preamble, 2006).

In March 2015, the IARC evaluated the carcinogenic potential of glyphosate. The IARC determined that there was a positive trend in the incidence of a rare tumor type, renal tubular carcinoma and renal tubule adenoma or carcinoma (combined) in males in one feeding study in CD-1 mice. A second study reported a positive trend for hemangiosarcomas in male CD-1 mice. Thus, in accordance with one of the preamble criteria, "the occurrence of tumors in two studies in one species," IARC determined that there is "sufficient evidence" in experimental animals for the carcinogenicity of glyphosate (IARC, 2015).

In contrast, the USEPA's carcinogenicity classification is based on weight-of-evidence considerations in accordance with the agency's 2005 Guidelines for Carcinogen Risk Assessment. The cancer guideline emphasizes the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. This evaluation is accomplished in a single integrative step after assessing all of the individual lines of evidence. Evidence considered includes tumor findings, or lack thereof, in humans and laboratory animals; an agent's chemical and physical properties; its structure-activity relationships (SARs) as compared with other carcinogenic agents; and studies addressing potential carcinogenic processes and mode(s) of action, either *in vivo* or *in vitro*. Data from epidemiological studies are generally preferred for characterizing human cancer hazard and risk. However, all of the information discussed above could provide valuable insight into the possible mode(s) of action and likelihood of human cancer hazard and risk (USEPA, 2005).

Conclusions for evidence of carcinogenicity are based on the combined strength and coherence of inferences appropriately drawn from all of the available information. The following observations add significance to the tumor findings: tumors in multiple species, strains, or both sexes; dose-related increases; progression of lesions from pre-neoplastic to benign to malignant; proportion of malignant tumors; reduced latency of neoplastic lesions; and both biological and statistical significance of the findings (USEPA, 2005).

The IARC attributed the kidney tumors observed in male CD-1 mice at the high dose in the feeding study (MRID No. 00251007) to treatment since they are rare and there was borderline significance in trend test (P=0.034 for carcinoma and P=0.037 for combined adenoma or carcinoma) in a Cochran-Armitage trend test. However, as shown in Table 14, the agency's statistical analyses did not show a significant trend for either carcinoma (P=0.06345) or the combined adenoma or carcinoma (P=0.06483). In a Fisher's exact test, when compared to the concurrent control, there was no pairwise significance for any tumor type (adenoma, carcinoma, or combined). There were no pre-neoplastic renal tubular lesions such as tubular necrosis/ regeneration, hyperplasia or hypertrophy, despite a high dose level (4945 mg/kg/day) that was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guidelines. Examination of multiple sections of kidneys from all animals by more than one pathologist did not result in any additional neoplasms. Although the highest dose tested (4945 mg/kg/day) was approximately 5-fold higher than the limit dose (1000 mg/kg/day) recommended by the agency's guideline, the incidence of the kidney tumors was minimal (1/50 adenomas and 2/50 carcinomas) compared to controls (1/49 adenomas). An evaluation by the PWG concluded that the renal tumors are not treatment-related since there were no compound related nephrotoxic lesions, including pre-neoplastic changes, multiple tumors were not found in any animals, and there was no evidence of a significant linear trend at the 0.5 level in a one-tailed Cochran-Armitage test or pairwise significance in a Fisher's exact test. Furthermore, kidney tumors were not seen when tested at lower (85 to 1000 mg/kg/day) doses or at a comparable (4116 mg/kg/day) dose in this strain of mice in the other three studies. Thus, the totality of data available from 4 carcinogenicity studies provides a strong support for the conclusion that the kidney tumors seen in one study is not the result of a carcinogenic response to glyphosate.

The IARC attributed the hemangiosarcomas observed in male CD-1 mice at the high dose in separate feeding study (MRID No. 49631702) to treatment due to the positive trend (P<0.001) in a Cochran-Armitage trend test. As shown in Table 16, the agency's statistical analyses also showed a positive trend (P=0.00296) in the trend test. In the Fisher's exact test, there was no pairwise significance when compared to controls. In contrast with the IARC, the CARC did not consider the hemangiosarcomas to be treatment-related based on the following weight-of-evidence considerations: 1) there was no pairwise significance; 2) lack of dose-response; 3) the incidence was near the upper limit (0–8%) of the background rate at the performing laboratory; 4) hemangiosarcomas are commonly observed as spontaneous tumors in male CD-1 strain mice; and 5) hemangiosarcomas were not seen when tested at comparable doses (946–1467 mg/kg/day) or at considerably higher doses (4116–4945 mg/kg/day) in this strain of mice in the other studies (MRID No.00251007, Arysta, 1997b, Nufarm, 2009b). It is noted that JMPR in their evaluation also concluded that the hemangiosarcomas are not treatment-related owing to lack of dose-response relationship, lack of statistical significance and incidences within the historical control range (JMPR, 2004).

Hemangiosarcomas have similar histopathological features in rodents and humans but differ in both incidence and tissue site. In human populations, hemangiosarcomas have an incidence rate of approximately 0.2 new cases/100,000 people (0.0002%) (1996–2000, US National Cancer Institute–SEER Database) and account for <1% of all human sarcomas. The historical background incidence of hemangiosarcomas in B6C3F1 and CD-1 mice relative to the incidence rate in humans has thus been estimated to be approximately 10,000-fold higher than in people (Pegg *et al.,* 2012). The most common sites for spontaneous hemangiosarcomas in rodents are liver, spleen, bone marrow, and to a lesser extent in lymph nodes and skin (see references in Pegg *et al.* (2012). In male mice, liver and spleen tend to be the most common sites. Human hemangiosarcoma is most commonly reported in skin (Weiss *et al.*, 2001). Primary liver hemangiosarcoma in humans has been linked to chemical exposure, notably thorotrast and vinyl chloride, which are both considered genotoxic carcinogens. There are several examples of induction of hemangiosarcomas by non-genotoxic agents in mice, but no clear examples of hemangiosarcoma induction by non-genotoxic agents in human populations (Cohen *et al.,* 2009). Several studies have looked at potential mode of action (MOA) for these tumors in mice in response to various drugs or chemicals. These MOAs generally relate to hypoxia or vascular toxicity as early key events.

1. Mutagenicity

Glyphosate was not mutagenic in bacteria or mammalian cells *in vitro*. Additionally, glyphosate did not induce chromosomal aberrations *in vitro*. Although some studies in the open literature reported positive findings for micronuclei induction in rodents, these findings were not replicated in the majority of the rodent micronucleus assay studies. There is no convincing evidence that the DNA damage is a direct effect of glyphosate, but under some conditions may be secondary to cytotoxicity or oxidative damage. Furthermore, the chemical structure of glyphosate, with its absence of alkyl groups also provides SAR support for the lack of mutagenic/genotoxic potential.

IARC concluded that "there is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic"; however, the IARC analysis included studies that tested glyphosate-formulated products as well as studies where the test material was not well-characterized (*i.e.*, no purity information was provided). The CARC did not include such studies in their evaluation. The IARC analysis also focused on DNA damage as an endpoint (*e.g.*, comet assay); however, DNA damage is often reversible and can result from events that are secondary to toxicity (cytotoxicity), as opposed to permanent DNA changes which are detected in tests for mutations and chromosomal damage (*e.g.* chromosomal aberrations or micronuclei induction). The studies that IARC cited, where positive findings were reported for chromosomal damage, had study limitations confounding the interpretation of the results. In addition, these positive findings were not reproduced in other guideline or guideline-like studies evaluating the same endpoints. This includes many negative studies cited by Kier and Kirkland (2013) that were considered by CARC, but were not included in the IARC decision.

2. Structure Activity Relationship

Sulfosate (the trimethylsulfonium salt of glyphosate) is classified as a Group E Chemical: "Not Likely to be Carcinogenic to Humans," based on the lack of evidence of carcinogenicity in mice and rats in two acceptable studies, and absence of mutagenicity concern.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the 2005 Guidelines for Carcinogen Risk Assessment, glyphosate is classified as "Not Likely to be Carcinogenic to Humans." This classification is based on the following weight-of-evidence considerations:

- The epidemiological evidence at this time does not support a causal relationship between glyphosate exposure and solid tumors. There is also no evidence to support a causal relationship between glyphosate exposure and the following non-solid tumors: leukemia, multiple myeloma, or Hodgkin lymphoma. The epidemiological evidence at this time is inconclusive for a causal or clear associative relationship between glyphosate and NHL. Multiple case-control studies and one prospective cohort study found no association; whereas, results from a small number of case-control studies (mostly in Sweden) did suggest an association. Limitations for most of these studies include small sample size, limited power, risk ratios with large confidence intervals, and recall bias as well as missing data. The literature will continue to be monitored for studies related to glyphosate and risk of NHL.

- In experimental animals, there is no evidence for carcinogenicity. Dietary administration of glyphosate at doses ranging from 3.0 to 1500 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in seven separate studies with male or female Sprague-Dawley or Wistar rats. Similarly, dietary administration of glyphosate at

doses ranging from 85 to 4945 mg/kg/day for up to two years produced no evidence of carcinogenic response to treatment in four separate studies with male or female CD-1 mice. The CARC did not consider any of the observed tumors in 11 carcinogenicity studies in rats and mice to be treatment-related since the observed tumors did not exhibit a clear dose-response relationship, were not supported pre-neoplastic changes (*e.g.*, foci, hypertrophy, and hyperplasia), were not statistically significant on pairwise statistical analysis, and/or were within the range of the historical control data.

- Based on a weight of evidence approach from a wide range of assays both *in vitro* and *in vivo* including endpoints for gene mutation, chromosomal damage, DNA damage and repair, there is no *in vivo* genotoxic or mutagenic concern for glyphosate.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Not required.

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Cc: Wise, Louise[Wise.Louise@epa.gov]
To: Mojica, Andrea[Mojica.andrea@epa.gov]
From: Jones, Jim
Sent: Tue 11/3/2015 5:40:16 PM
Subject: Re: materials for Tom B glyphosate meeting

Yes

Sent from my iPhone

> On Nov 3, 2015, at 12:19 PM, Mojica, Andrea <Mojica.andrea@epa.gov> wrote:
>
> Jim,
>
> Attached are the materials for the Tom B glyphosate briefing. The relevant cancer slides from your briefing last week and the glyphosate CARC document from October 1, 2015. OK to send to ORD?
>
> Thanks,
>
> Andrea
>
>
>
> <417300_2015-10-01_TXR0057299.pdf>
> <TB Brief Glyphosate JR 11 3 15.pptx>

To: Bahadori, Tina[Bahadori.Tina@epa.gov]
Cc: Kavlock, Robert[Kavlock.Robert@epa.gov]
From: Gentry, Nathan
Sent: Tue 11/3/2015 8:59:37 PM
Subject: RE: Draft Human Health Risk Assessment for Glyphosate

I haven't forwarded the invite to anyone besides you and Bob, and I don't believe we ever gave OCSPP a list of names (that's why I asked). I can forward to whoever you'd like.

Nathan Gentry

Scheduler for Tom Burke, Lek Kadeli and Bob Kavlock

EPA Office of Research and Development

Phone: 202-564-9084

Fax: 202-565-2430

From: Bahadori, Tina
Sent: Tuesday, November 03, 2015 3:57 PM
To: Gentry, Nathan <Gentry.Nathan@epa.gov>
Cc: Kavlock, Robert <Kavlock.Robert@epa.gov>
Subject: RE: Draft Human Health Risk Assessment for Glyphosate

Nathan,

I noticed several NHEERL names on the invite – Charles Wood and Danelle Lobdell. Were they on the original OCSPP invite? If they were, I want to direct OSP to them for this additional peer review. If Bob agrees, Bob Fegley should be included in the invite too.

Tina

From: Gentry, Nathan
Sent: Tuesday, November 03, 2015 2:01 PM
To: Kavlock, Robert <Kavlock.Robert@epa.gov>; Burke, Thomas <Burke.Thomas@epa.gov>
Cc: Bahadori, Tina <Bahadori.Tina@epa.gov>; Deener, Kathleen <Deener.Kathleen@epa.gov>; Gwinn, Maureen <gwinn.maureen@epa.gov>

Subject: RE: Draft Human Health Risk Assessment for Glyphosate

There's a big meeting on Thursday with OCSPP and Tom. Who from ORD should be included? Bob, do you want to be added?

Nathan Gentry

Scheduler for Tom Burke, Lek Kadeli and Bob Kavlock

EPA Office of Research and Development

Phone: 202-564-9084

Fax: 202-565-2430

From: Kavlock, Robert
Sent: Tuesday, November 03, 2015 12:01 PM
To: Burke, Thomas <Burke.Thomas@epa.gov>
Cc: Bahadori, Tina <Bahadori.Tina@epa.gov>; Deener, Kathleen <Deener.Kathleen@epa.gov>; Gwinn, Maureen <gwinn.maureen@epa.gov>
Subject: Re: Draft Human Health Risk Assessment for Glyphosate

Yep.

On Nov 3, 2015, at 5:10 PM, Burke, Thomas <Burke.Thomas@epa.gov> wrote:

> Sounds good
>
> Thomas A. Burke, PhD, MPH
>
> Deputy Assistant Administrator
>
> EPA Science Advisor
>
> Office of Research and Development

202-564-6620

burke.thomas@epa.gov

On Nov 3, 2015, at 9:20 AM, Bahadori, Tina <Bahadori.Tina@epa.gov> wrote:

> We are going for NCEA, NERL, NHEERL, NCCT. I think that covers it, right?
> T.
>
> **From:** Deener, Kathleen
> **Sent:** Tuesday, November 03, 2015 10:19 AM
> **To:** Bahadori, Tina <Bahadori.Tina@epa.gov>
> **Cc:** Burke, Thomas <Burke.Thomas@epa.gov>; Kavlock, Robert <Kavlock.Robert@epa.gov>; Gwinn, Maureen <gwinn.maureen@epa.gov>
> **Subject:** Re: Draft Human Health Risk Assessment for Glyphosate
>
> Could be helpful to pull in someone from NCEA too.
>
> Sent from my iPhone
>
> On Nov 3, 2015, at 9:16 AM, Bahadori, Tina <Bahadori.Tina@epa.gov> wrote:
>
> > Ok, we will also ask Matt Martin from NCCT to review, since he was on the IARC glyphosate committee.
> >
> > T.
> >
> > **From:** Burke, Thomas
> > **Sent:** Tuesday, November 03, 2015 9:56 AM
> > **To:** Bahadori, Tina <Bahadori.Tina@epa.gov>
> > **Cc:** Kavlock, Robert <Kavlock.Robert@epa.gov>; Deener, Kathleen <Deener.Kathleen@epa.gov>; Gwinn, Maureen <gwinn.maureen@epa.gov>
> > **Subject:** Re: Draft Human Health Risk Assessment for Glyphosate
> >
> > This is very important. Let's make sure we get the right folks to assist. I am very interested in the cancer review and conclusions.

Tom

Thomas A. Burke, PhD, MPH

Deputy Assistant Administrator

EPA Science Advisor

Office of Research and Development

202-564-6620

burke.thomas@epa.gov

On Nov 3, 2015, at 8:26 AM, Bahadori, Tina <Bahadori.Tina@epa.gov> wrote:

Good morning/afternoon,

Ex. 5 - Deliberative Process

Tina

From: Smith, Charles
Sent: Tuesday, November 03, 2015 8:17 AM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Vogel, Dana <Vogel.Dana@epa.gov>; Dawson, Jeffrey <Dawson.Jeff@epa.gov>; Rowland, Jess <Rowland.Jess@epa.gov>
Subject: Draft Human Health Risk Assessment for Glyphosate

Tina,

Attached you will find the draft human health risk assessment for glyphosate as well as the recently completed cancer review (CARC) document. I

believe Dana had contacted you to let you know that we would be sending this to you.

Ex. 5 - Deliberative Process

Please feel free to contact me via email or phone if you have any specific questions about the risk assessment or how it was performed. Thanks and have a great day!

Charles " Billy" Smith

Branch Chief RAB1

Health Effects Division

Office of Pesticide Programs

703-305-0291

<417300_2015-10-01_TXR0057299.pdf>

<Glyohosate Draft Final Risk assessment - 2-Nov-2015 (II).docx>

To: Gentry, Nathan[Gentry.Nathan@epa.gov]
Cc: Kavlock, Robert[Kavlock.Robert@epa.gov]
From: Bahadori, Tina
Sent: Tue 11/3/2015 8:57:05 PM
Subject: RE: Draft Human Health Risk Assessment for Glyphosate

Nathan,

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To: Kavlock, Robert <Kavlock.Robert@epa.gov>; Burke, Thomas <Burke.Thomas@epa.gov>
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Scheduler for Tom Burke, Lek Kadeli and Bob Kavlock

EPA Office of Research and Development

Phone: 202-564-9084

Fax: 202-565-2430

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Cc: Bahadori, Tina <Bahadori.Tina@epa.gov>; Deener, Kathleen <Deener.Kathleen@epa.gov>;

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> Deputy Assistant Administrator
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> EPA Science Advisor
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> Office of Research and Development
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> burke.thomas@epa.gov
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Subject: Re: Draft Human Health Risk Assessment for Glyphosate

This is very important. Let's make sure we get the right folks to assist. I am very interested in the cancer review and conclusions.

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Thomas A. Burke, PhD, MPH

Deputy Assistant Administrator

EPA Science Advisor

Office of Research and Development

202-564-6620

burke.thomas@epa.gov

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Tina

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To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Vogel, Dana <Vogel.Dana@epa.gov>; Dawson, Jeffrey <Dawson.Jeff@epa.gov>; Rowland, Jess <Rowland.Jess@epa.gov>
Subject: Draft Human Health Risk Assessment for Glyphosate

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Ex. 5 - Deliberative Process

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Charles " Billy" Smith

Branch Chief RAB1

Health Effects Division

Office of Pesticide Programs

703-305-0291

<417300_2015-10-01_TXR0057299.pdf>

<Glyohosate Draft Final Risk assessment - 2-Nov-2015 (II).docx>

To: Kavlock, Robert[Kavlock.Robert@epa.gov]
Cc: Gwinn, Maureen[gwinn.maureen@epa.gov]
From: Bahadori, Tina
Sent: Tue 11/3/2015 3:17:47 PM
Subject: RE: Draft Human Health Risk Assessment for Glyphosate

Yes, I am working with Fegley and McQueen in OSP.

From: Kavlock, Robert
Sent: Tuesday, November 03, 2015 10:00 AM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Burke, Thomas <Burke.Thomas@epa.gov>; Deener, Kathleen <Deener.Kathleen@epa.gov>; Gwinn, Maureen <gwinn.maureen@epa.gov>
Subject: Re: Draft Human Health Risk Assessment for Glyphosate

Tina

Make sure Fegley sees this as well.

On Nov 3, 2015, at 3:25 PM, Bahadori, Tina <Bahadori.Tina@epa.gov> wrote:

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Ex. 5 - Deliberative Process

Tina

From: Smith, Charles
Sent: Tuesday, November 03, 2015 8:17 AM

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Cc: Vogel, Dana <Vogel.Dana@epa.gov>; Dawson, Jeffrey <Dawson.Jeff@epa.gov>; Rowland, Jess <Rowland.Jess@epa.gov>
Subject: Draft Human Health Risk Assessment for Glyphosate

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Charles " Billy" Smith

Branch Chief RAB1

Health Effects Division

Office of Pesticide Programs

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<417300_2015-10-01_TXR0057299.pdf>

<Glyohosate Draft Final Risk assessment - 2-Nov-2015 (II).docx>

To: Keigwin, Richard[Keigwin.Richard@epa.gov]; Sisco, Debby[Sisco.Debby@epa.gov]; Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Overstreet, Anne[overstreet.anne@epa.gov]; Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Keltz, Colleen[Keltz.Colleen@epa.gov]; Han, Kaythi[Han.Kaythi@epa.gov]
From: Strauss, Linda
Sent: Mon 5/2/2016 9:08:50 PM
Subject: FW: DESK STATEMENT Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Thanks, all. Thanks. Spoke to Rick then Jim and here's what we agreed to send.
Linda

From: Strauss, Linda
Sent: Monday, May 02, 2016 5:07 PM
To: Harrison, Melissa <Harrison.Melissa@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: FW: DESK STATEMENT Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

To: Jones, Jim[Jones.Jim@epa.gov]
Cc: Keigwin, Richard[Keigwin.Richard@epa.gov]
From: Strauss, Linda
Sent: Mon 5/2/2016 9:03:56 PM
Subject: FW: DESK STATEMENT - this OK TO GO? Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

+ Rick

Ex. 5 - Deliberative Process

From: Keigwin, Richard
Sent: Monday, May 02, 2016 3:51 PM
To: Sisco, Debby <Sisco.Debby@epa.gov>
Cc: Keltz, Colleen <Keltz.Colleen@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Rick Keigwin
Deputy Director for Programs
Office of Pesticide Programs
US Environmental Protection Agency

Sent from my Windows Phone

From: Sisco, Debby
Sent: 5/2/2016 3:04 PM
To: Keigwin, Richard
Cc: Keltz, Colleen; Dinkins, Darlene; Strauss, Linda; Han, Kaythi
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Debby Sisco

Office of Pesticide Programs (7501P)

Ethics Officer and Special Assistant to the Director
Room 12651 Potomac Yard South (office: 703 308-8121; cell: 571 317-4823)

From: Han, Kaythi
Sent: Monday, May 02, 2016 2:53 PM
To: Sisco, Debby <Sisco.Debby@epa.gov>
Cc: Keltz, Colleen <Keltz.Colleen@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

From: Sisco, Debby
Sent: Monday, May 02, 2016 2:40 PM
To: Han, Kaythi <Han.Kaythi@epa.gov>
Cc: Keltz, Colleen <Keltz.Colleen@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Debby Sisco

Office of Pesticide Programs (7501P)
Ethics Officer and Special Assistant to the Director
Room 12651 Potomac Yard South (office: 703 308-8121; cell: 571 317-4823)

From: Han, Kaythi

Sent: Monday, May 02, 2016 2:22 PM
To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Hi Cathy,

Ex. 5 - Deliberative Process

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 2:13 PM
To: Han, Kaythi <Han.Kaythi@epa.gov>
Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Catherine C. Milbourn

U.S. EPA HQ

Office of the Administrator

Office of Media Relations

202-564-7849 (office)

202-420-8648 (mobile)

Milbourn.cathy@epa.gov

From: Han, Kaythi
Sent: Monday, May 02, 2016 1:39 PM
To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Hi Cathy,

The reporter can find the PDF of the IARC report at:
http://monographs.iarc.fr/ENG/Monographs/vol112/

Kaythi

From: Strauss, Linda
Sent: Monday, May 02, 2016 1:33 PM
To: Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Can you all let Cathy know? Thanks.

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 1:28 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: FW: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Good afternoon,

I am a legal reporter at Bloomberg who has a story out about a lawsuit filed against Quaker Oats containing trace levels of glyphosate. Could you please send me the recent report of the CARC review about glyphosate?

Thanks,

Rebecca

To: Strauss, Linda[Strauss.Linda@epa.gov]
Cc: Keigwin, Richard[Keigwin.Richard@epa.gov]; Han, Kaythi[Han.Kaythi@epa.gov]
From: Keltz, Colleen
Sent: Mon 5/2/2016 8:58:23 PM
Subject: RE: DESK STATEMENT - this OK TO GO? Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

From: Strauss, Linda
Sent: Monday, May 02, 2016 4:52 PM
To: Jones, Jim <Jones.Jim@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>
Subject: DESK STATEMENT - this OK TO GO? Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

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From: Keigwin, Richard
Sent: Monday, May 02, 2016 3:51 PM
To: Sisco, Debby <Sisco.Debby@epa.gov>
Cc: Keltz, Colleen <Keltz.Colleen@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Rick Keigwin
Deputy Director for Programs
Office of Pesticide Programs
US Environmental Protection Agency

Sent from my Windows Phone

From: Sisco, Debby
Sent: 5/2/2016 3:04 PM
To: Keigwin, Richard
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Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

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Ethics Officer and Special Assistant to the Director
Room 12651 Potomac Yard South (office: 703 308-8121; cell: 571 317-4823)

From: Han, Kaythi
Sent: Monday, May 02, 2016 2:53 PM
To: Sisco, Debby <Sisco.Debby@epa.gov>
Cc: Keltz, Colleen <Keltz.Colleen@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

From: Sisco, Debby
Sent: Monday, May 02, 2016 2:40 PM
To: Han, Kaythi <Han.Kaythi@epa.gov>
Cc: Keltz, Colleen <Keltz.Colleen@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
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Ex. 5 - Deliberative Process

Debby Sisco

Office of Pesticide Programs (7501P)
Ethics Officer and Special Assistant to the Director

Room 12651 Potomac Yard South (office: 703 308-8121; cell: 571 317-4823)

From: Han, Kaythi
Sent: Monday, May 02, 2016 2:22 PM
To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>
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Hi Cathy,

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Sent: Monday, May 02, 2016 2:13 PM

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Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>
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Ex. 5 - Deliberative Process

Catherine C. Milbourn

U.S. EPA HQ

Office of the Administrator

Office of Media Relations

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202-420-8648 (mobile)

Milbourn.cathy@epa.gov

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Thanks,

Rebecca

To: Jones, Jim[Jones.Jim@epa.gov]; Keigwin, Richard[Keigwin.Richard@epa.gov]; Sisco, Debby[Sisco.Debby@epa.gov]; Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Han, Kaythi[Han.Kaythi@epa.gov]; Keltz, Colleen[Keltz.Colleen@epa.gov]; Wise, Louise[Wise.Louise@epa.gov]; Perlis, Robert[Perlis.Robert@epa.gov]
From: Strauss, Linda
Sent: Mon 5/2/2016 8:53:55 PM
Subject: RE: DESK STATEMENT - this OK TO GO NOW? Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

+ Bob P

From: Strauss, Linda
Sent: Monday, May 02, 2016 4:52 PM
To: Jones, Jim <Jones.Jim@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>
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Ex. 5 - Deliberative Process

Rick Keigwin
Deputy Director for Programs
Office of Pesticide Programs
US Environmental Protection Agency

Sent from my Windows Phone

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Sent: 5/2/2016 3:04 PM
To: Keigwin, Richard
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Kaythi

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Thanks,

Rebecca

To: Keigwin, Richard[Keigwin.Richard@epa.gov]
From: Sisco, Debby
Sent: Mon 5/2/2016 8:45:26 PM
Subject: Fwd: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

Sent from my iPhone

Begin forwarded message:

From: "Anderson, Neil" <Anderson.Neil@epa.gov>
Date: May 2, 2016 at 4:40:55 PM EDT
To: "Han, Kaythi" <Han.Kaythi@epa.gov>, "Nguyen, Khue" <Nguyen.Khue@epa.gov>, "Ingram, Earl" <Ingram.Earl@epa.gov>
Cc: "Sisco, Debby" <Sisco.Debby@epa.gov>, "Dinkins, Darlene" <Dinkins.Darlene@epa.gov>, "Keltz, Colleen" <Keltz.Colleen@epa.gov>
Subject: RE: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

Ex. 5 - Deliberative Process

From: Han, Kaythi
Sent: Monday, May 02, 2016 4:35 PM
To: Anderson, Neil <Anderson.Neil@epa.gov>; Nguyen, Khue <Nguyen.Khue@epa.gov>; Ingram, Earl <Ingram.Earl@epa.gov>
Cc: Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>
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Importance: High

Ex. 5 - Deliberative Process

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From: Strauss, Linda
Sent: Monday, May 02, 2016 4:14 PM
To: Keigwin, Richard <Keigwin.Richard@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>
Subject: FW: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 4:12 PM
To: Conger, Nick <Conger.Nick@epa.gov>; Harrison, Melissa <Harrison.Melissa@epa.gov>; Perry, Dale <Perry.Dale@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Hull, George <Hull.George@epa.gov>
Subject: RE: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

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To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Harrison, Melissa <Harrison.Melissa@epa.gov>; Perry, Dale <Perry.Dale@epa.gov>
Cc: Hull, George <Hull.George@epa.gov>
Subject: RE: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

Thanks Cathy.

Ex. 5 - Deliberative Process

Nick Conger

U.S. Environmental Protection Agency

Office: (202) 564-6287

Cell: (202) 412-2655

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 3:34 PM
To: Harrison, Melissa <Harrison.Melissa@epa.gov>; Conger, Nick <Conger.Nick@epa.gov>; Perry, Dale <Perry.Dale@epa.gov>
Cc: Hull, George <Hull.George@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>
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Ex. 5 - Deliberative Process

Outlets asking:

WSJ

Bloomberg

Bloomberg/BNA

Reuters Freelancer

Agi- pulse

Freelancer

http://biologicaldiversity.org/news/press_releases/2016/glyphosate-05-02-2016.html

<image001.gif>

For Immediate Release, May 2, 2016

Contact: Nathan Donley, (971) 717-6406, ndonley@biologicaldiversity.org

EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

PORTLAND, *Ore.*— An EPA analysis relying heavily on unpublished, industry funded studies has determined that glyphosate, commonly known as Roundup, is "not likely to be carcinogenic to humans." The EPA determination, released to the public on Friday, stands in sharp contrast to a finding last year by the World Health Organization's cancer-research arm that glyphosate is a probable human carcinogen.

"EPA's determination that glyphosate is non-carcinogenic is disappointing, but not terribly surprising — industry has been manipulating this process for years," said Nathan Donley, a scientist with the Center for Biological Diversity. "The analysis done by the World Health Organization is more open and transparent and remains the gold standard."

The EPA's analysis relied heavily on industry-funded studies that have not undergone public scrutiny, while the WHO used publically available research for its analysis. Furthermore, the WHO took into account studies on actual products that are available on store shelves, while the EPA ignored those studies to focus solely on studies that tested glyphosate as a single ingredient. Most products containing glyphosate have other ingredients that can make the pesticide more dangerous.

"We shouldn't gamble with the risk of cancer and must take appropriate precautions until we get a conclusive answer about the true dangers of glyphosate," said Donley. "The indiscriminate drenching of

farms, ball fields and backyards with glyphosate needs to end."

The EPA's industry-friendly determination comes amid a fierce debate in Europe and the United States over the safety of glyphosate.

In February 35 members of the U.S. House of Representatives sent a letter to EPA Administrator Gina McCarthy expressing concerns regarding the potential negative health and environmental impacts of a pesticide, Enlist Duo, that combines glyphosate and 2,4-D. The agency is currently reanalyzing its decision to register the dangerous pesticide after it was revealed that the industry had withheld data on how the pesticides work in combination with other ingredients to have a stronger effect on the environment.

This finding comes as the EPA is in undertaking a "registration review" of glyphosate, a process designed to determine whether the chemical can safely be used in light of new scientific research. These documents will inform the agency's decision on whether to allow glyphosate to be used for the next 15 years. The last time the EPA fully analyzed the threats posed by glyphosate was 1993.

The Center for Biological Diversity is a national, nonprofit conservation organization with more than 1 million members and online activists dedicated to the protection of endangered species and wild places.

<image002.gif>

To: Keigwin, Richard[Keigwin.Richard@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]
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Date: May 2, 2016 at 4:36:00 PM EDT
To: "Sisco, Debby" <Sisco.Debby@epa.gov>, "Han, Kaythi" <Han.Kaythi@epa.gov>
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I passed on Ricks input toDarlene.

Sent from my iPhone

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Subject: FW: Glyphosate blowing up. FW: Press Release: EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 4:12 PM
To: Conger, Nick <Conger.Nick@epa.gov>; Harrison, Melissa <Harrison.Melissa@epa.gov>; Perry, Dale <Perry.Dale@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
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Nick Conger

U.S. Environmental Protection Agency

Office: (202) 564-6287

Cell: (202) 412-2655

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Outlets asking:

WSJ

Bloomberg

Bloomberg/BNA

Reuters Freelancer

Agi- pulse

Freelancer

http://biologicaldiversity.org/news/press_releases/2016/glyphosate-05-02-2016.html

CENTER for BIOLOGICAL DIVERSITY Because

For Immediate Release, May 2, 2016

Contact: Nathan Donley, (971) 717-6406, ndonley@biologicaldiversity.org

EPA Uses Industry-funded Studies to Determine Glyphosate Does Not Cause Cancer

PORTLAND, *Ore.*— An EPA analysis relying heavily on unpublished, industry funded studies has determined that glyphosate, commonly known as Roundup, is "not likely to be carcinogenic to humans." The EPA determination, released to the public on Friday, stands in sharp contrast to a finding last year by the World Health Organization's cancer-research arm that glyphosate is a probable human carcinogen.

"EPA's determination that glyphosate is non-carcinogenic is disappointing, but not terribly surprising — industry has been manipulating this process for years," said Nathan Donley, a scientist with the Center for Biological Diversity. "The analysis done by the World Health Organization is more open and transparent and remains the gold standard."

The EPA's analysis relied heavily on industry-funded studies that have not undergone public scrutiny, while the WHO used publically available research for its analysis. Furthermore, the WHO took into account studies on actual products that are available on store shelves, while the EPA ignored those studies to focus solely on studies that tested glyphosate as a single ingredient. Most products containing glyphosate have other ingredients that can make the pesticide more dangerous.

"We shouldn't gamble with the risk of cancer and must take appropriate precautions until we get a conclusive answer about the true dangers of glyphosate," said Donley. "The indiscriminate drenching of farms, ball fields and backyards with glyphosate needs to end."

The EPA's industry-friendly determination comes amid a fierce debate in Europe and the United States over the safety of glyphosate.

In February 35 members of the U.S. House of Representatives sent a letter to EPA Administrator Gina McCarthy expressing concerns regarding the potential negative health and environmental impacts of a pesticide, Enlist Duo, that combines glyphosate and 2,4-D. The agency is currently reanalyzing its decision to register the dangerous pesticide after it was revealed that the industry had withheld data on how the pesticides work in combination with other ingredients to have a stronger effect on the environment.

This finding comes as the EPA is in undertaking a "registration review" of glyphosate, a process designed to determine whether the chemical can safely be used in light of new scientific research. These documents will inform the agency's decision on whether to allow glyphosate to be used for the next 15 years. The last time the EPA fully analyzed the threats posed by glyphosate was 1993.

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Sent: Fri 3/20/2015 6:17:17 PM
Subject: IARC glyphosate released

FYI

http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

They fail to mention EPA's 2013 conclusion.

Dan Jenkins
US Agency Lead
Monsanto Company
202.383.2851 office
571.732.6575 cell

To: Housenger, Jack[Housenger.Jack@epa.gov]; Mojica, Andrea[Mojica.andrea@epa.gov]; Jones, Jim[Jones.Jim@epa.gov]
Cc: Wise, Louise[Wise.Louise@epa.gov]; Perlis, Robert[Perlis.Robert@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]; Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Sisco, Debby[Sisco.Debby@epa.gov]
From: Keigwin, Richard
Sent: Tue 5/10/2016 5:33:23 PM
Subject: RE: glyphosate draft response for review

No other comments from me.

From: Housenger, Jack
Sent: Tuesday, May 10, 2016 1:32 PM
To: Mojica, Andrea <Mojica.andrea@epa.gov>; Jones, Jim <Jones.Jim@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: Wise, Louise <Wise.Louise@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: RE: glyphosate draft response for review

Ex. 5 - Deliberative Process/Attorney-Client

From: Mojica, Andrea
Sent: Tuesday, May 10, 2016 1:03 PM
To: Jones, Jim <Jones.Jim@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: Housenger, Jack <Housenger.Jack@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: RE: glyphosate draft response for review

Ex. 5 - Deliberative Process/Attorney-Client

From: Jones, Jim
Sent: Tuesday, May 10, 2016 12:15 PM
To: Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: Housenger, Jack <Housenger.Jack@epa.gov>; Mojica, Andrea <Mojica.andrea@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: Re: glyphosate draft response for review

Thx Rick. Jim

Sent from my iPhone

On May 10, 2016, at 10:48 AM, Keigwin, Richard <Keigwin.Richard@epa.gov> wrote:

Ex. 5 - Deliberative Process/Attorney-Client

From: Housenger, Jack
Sent: Tuesday, May 10, 2016 10:45 AM
To: Mojica, Andrea <Mojica.andrea@epa.gov>; Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>

Subject: RE: glyphosate draft response for review

A few comments

From: Mojica, Andrea
Sent: Tuesday, May 10, 2016 10:32 AM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Perlis, Robert <Perlis.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>; Housenger, Jack <Housenger.Jack@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>
Subject: glyphosate draft response for review

All,

Attached is a draft response to Chairman Lamar Smith's (Committee on Science, Space, and Technology) glyphosate inquiry. I have attached in the incoming letter to the Administrator as well. Please let me know if you have any comments by May 12th.

Thanks,

Andrea

To: Sisco, Debby[Sisco.Debby@epa.gov]
Cc: Keltz, Colleen[Keltz.Colleen@epa.gov]; Dinkins, Darlene[Dinkins.Darlene@epa.gov]; Strauss, Linda[Strauss.Linda@epa.gov]; Han, Kaythi[Han.Kaythi@epa.gov]
From: Keigwin, Richard
Sent: Mon 5/2/2016 7:51:17 PM
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Rick Keigwin
Deputy Director for Programs
Office of Pesticide Programs
US Environmental Protection Agency

Sent from my Windows Phone

From: Sisco, Debby
Sent: 5/2/2016 3:04 PM
To: Keigwin, Richard
Cc: Keltz, Colleen; Dinkins, Darlene; Strauss, Linda; Han, Kaythi
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Debby Sisco

Office of Pesticide Programs (7501P)
Ethics Officer and Special Assistant to the Director
Room 12651 Potomac Yard South (office: 703 308-8121; cell: 571 317-4823)

From: Han, Kaythi

Sent: Monday, May 02, 2016 2:53 PM
To: Sisco, Debby <Sisco.Debby@epa.gov>
Cc: Keltz, Colleen <Keltz.Colleen@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

From: Sisco, Debby
Sent: Monday, May 02, 2016 2:40 PM
To: Han, Kaythi <Han.Kaythi@epa.gov>
Cc: Keltz, Colleen <Keltz.Colleen@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Debby Sisco

Office of Pesticide Programs (7501P)
Ethics Officer and Special Assistant to the Director
Room 12651 Potomac Yard South (office: 703 308-8121; cell: 571 317-4823)

From: Han, Kaythi
Sent: Monday, May 02, 2016 2:22 PM
To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Hi Cathy,

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 2:13 PM
To: Han, Kaythi <Han.Kaythi@epa.gov>
Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Catherine C. Milbourn

U.S. EPA HQ

Office of the Administrator

Office of Media Relations

202-564-7849 (office)

202-420-8648 (mobile)

Milbourn.cathy@epa.gov

From: Han, Kaythi
Sent: Monday, May 02, 2016 1:39 PM
To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Cc: Strauss, Linda <Strauss.Linda@epa.gov>; Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Hi Cathy,

The reporter can find the PDF of the IARC report at:
http://monographs.iarc.fr/ENG/Monographs/vol112/

Kaythi

From: Strauss, Linda
Sent: Monday, May 02, 2016 1:33 PM
To: Sisco, Debby <Sisco.Debby@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Han, Kaythi <Han.Kaythi@epa.gov>
Subject: RE: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Can you all let Cathy know? Thanks.

From: Milbourn, Cathy
Sent: Monday, May 02, 2016 1:28 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>

Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: FW: EPA's Cancer Assessment Review Committee on Glyphosate BLOOMBERG NEWS

Ex. 5 - Deliberative Process

Good afternoon,

I am a legal reporter at Bloomberg who has a story out about a lawsuit filed against Quaker Oats containing trace levels of glyphosate. Could you please send me the recent report of the CARC review about glyphosate?

Thanks,

Rebecca

To: Kent, Ray[Kent.Ray@epa.gov]
From: Rowland, Jess
Sent: Mon 9/28/2015 7:31:25 PM
Subject: RE: Glyphosate

Raymond

Thank You SO MUCH for ALL your help with this CARC effort. For the secondary reviews, help at the meeting, with the documents etc.

Regards

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Kent, Ray
Sent: Monday, September 28, 2015 3:05 PM
To: Rowland, Jess
Subject: RE: Glyphosate

Jess,

Ex. 5 - Deliberative Process

Ray

From: Rowland, Jess
Sent: Sunday, September 27, 2015 9:02 PM
To: Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Dunbar, Anwar; Kent, Ray; Liccione, John; Lobdell, Danelle; Middleton, Karlyn; McCarroll, Nancy; Wood, Charles
Subject: Glyphosate
Importance: High

Greg et al.,

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Jordan, William[Jordan.William@epa.gov]
Cc: Kent, Ray[Kent.Ray@epa.gov]
From: Miller, David
Sent: Tue 3/24/2015 6:53:51 PM
Subject: FW: German regulators responding to questions related to glyphosate/cancer
Glyphosate D417808 mem.pdf
Glyphosate IARC review- comments on references -rjk_DJM.docx

Ex. 5 - Deliberative Process

David.

From: Miller, David
Sent: Tuesday, March 24, 2015 12:39 PM
To: Jordan, William
Subject: RE: German regulators responding to questions related to glyphosate/cancer

Thanks.

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

David.

From: Jordan, William
Sent: Tuesday, March 24, 2015 12:25 PM
To: Miller, David
Subject: FW: German regulators responding to questions related to glyphosate/cancer

FYI

Bill

William Jordan

Deputy Director, Programs

Office of Pesticide Programs

U. S. Environmental Protection Agency

Phone: 703-305-1049

Fax: 703-308-4776

Mailing Address:
USEPA Headquarters
Clinton Building
1200 Pennsylvania Ave., NW
Mail Code (7501P)
Washington, DC 20460

Courier Address:
Potomac Yards South
2777 Crystal Drive
Room 12-235
Arlington, VA

From: Overstreet, Anne
Sent: Tuesday, March 24, 2015 10:31 AM
To: Sisco, Debby; Jordan, William; Strauss, Linda; Han, Kaythi; Dinkins, Darlene
Subject: German regulators responding to questions related to glyphosate/cancer

FYI – the information below was apparently from German regulators in response to inquiries related to glyphosate.

Anne Overstreet, Chief
Communication Services Branch
Field and External Affairs Division
Office of Pesticide Programs
Environmental Protection Agency
overstreet.anne@epa.gov
(703)308-8068

From: Goodis, Michael
Sent: Tuesday, March 24, 2015 10:26 AM
To: Overstreet, Anne
Subject: FW:

FYI to keep you in the loop

Michael L. Goodis, P.E.

Associate Director, Pesticide Re-evaluation Division (7508P)

Office of Pesticide Programs

US Environmental Protection Agency

Phone: 703-308-8157

goodis.michael@epa.gov

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, March 24, 2015 10:24 AM
To: JENKINS, DANIEL J [AG/1920]; Goodis, Michael
Cc: Keigwin, Richard; Cyran, Carissa; Rowland, Jess; Anderson, Neil; Housenger, Jack
Subject: RE:

The German Regulators have responded. We hope that EPA would consider the following in their approach to responses:

Does Glyphosate cause cancer?

(English translation of text at http://www.bfr.bund.de/cm/343/loest-glyphosat-krebs-aus.pdf)

Communication 007/2015 BfR March 23, 2015

Glyphosate, the ingredient in plant protection products, was deemed non-carcinogenic after review by national, European and other international institutions including the Joint Meeting on Pesticide Residues of the World Health Organisation and UN Food and Agriculture Organisation, of all the studies at their disposal.

At a meeting of the International Agency for Research on Cancer (IARC) of the World Health

Organization in Lyon in March 2015, experts gathered to discuss glyphosate and, based on the studies they looked at, came to a different classification, namely as a Group 2A carcinogen, or "probably" carcinogenic for humans. This Classification was published in a short report in the journal "Lancet" on March 20, 2015.

The (German) Federal Institute for Risk Assessment (BfR) was appointed EU rapporteur for glyphosate as part of the EU re-evaluation and is commenting on this IARC Classification on the basis of the summary that was published.

Seventeen experts from 11 countries met at the IARC in March 2015 to weigh the carcinogenicity or potential carcinogenicity of four organophosphates and glyphosate, none of which has been classified by the competent European authorities as carcinogenic or mutagenic.

On the basis of the information at the BfR's disposal, the classification of glyphosate in the Lancet on March 20 as belonging to Group 2A (probably carcinogenic to humans) is **scientifically hard to follow and apparently based on very few studies**. The IARC decision cannot be judged definitively, however, since the final IARC Monograph, in which its decision will be backed up with more information, is not yet published.

The recently published IARC classification is based partially on indications of carcinogenic effect in human studies, i.e. a statistical relationship between exposure to glyphosate and an increased risk of non-Hodgkin lymphomas. This risk is derived from three epidemiological studies from the USA, Canada and Sweden. However, this conclusion was not shared a very large scale "Agricultural Health Study", also cited, or by other studies. **In the current report of the BfR to the EU, on the other hand, over 30 epidemiological studies were evaluated. In the comprehensive opinion, there was no proven relationship between exposure to glyphosate and an increased risk of non-Hodgkin's lymphoma or other types of cancer.**

Furthermore, IARC advances findings from animal testing as proof of a carcinogenic effect of glyphosate. All of these findings were also considered in the glyphosate appraisals of the BfR, the EU institutions and the Joint Meeting on Pesticide Residues of the WHO and FAO, which is responsible for the appraisal of pesticide ingredients. These organizations came to the overall conclusion that glyphosate is not carcinogenic. The BfR does not know how many of the 11 long-term studies on rats and mice considered valid by the BfR were available to the IARC.

The theory advanced in one study that skin tumors could be caused by a highly concentrated, irritant formulation with the ingredient were also not regarded by the EU institutions as proof for the carcinogenic qualities of glyphosate.

Indications for a gene toxic potential of glyphosate cannot be concluded from IARC's published summary, since the review also included formulations that were not further described.

The fact that different bodies reach different conclusions from different information and interpretations of experimental data is a daily reality in risk assessment. The BfR will examine IARC'sclassification in detail once the Monograph is published.

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: JENKINS, DANIEL J [AG/1920]
Sent: Monday, March 23, 2015 10:10 AM
To: 'goodis.michael@epa.gov'
Cc: 'Keigwin, Richard'; 'Cyran, Carissa'; 'rowland.jess@epa.gov'; 'anderson.neil@epa.gov'
Subject:

Mike:

Per our phone conversation. We hope EPA will correct mistakes or absences of fact with respect to its record on glyphosate (including the 2013 statement and the AHS study) as it relates to carcinogenicity.

2009 EPA Glyphosate Reg Review

Carcinogenicity was not identified as a concern in the work plan
http://www.epa.gov/oppsrrd1/registration_review/glyphosate/

2013 Federal Register Notice (FR 25396 Vol. 78, No. 84, Wednesday, May 1, 2013) Final Rule new tolerances in or on multiple commodities: "EPA has concluded that glyphosate does not pose a cancer risk to humans."

http://www.gpo.gov/fdsys/pkg/FR-2013-05-01/pdf/2013-10316.pdf

"For the herbicide **glyphosate**, there was *limited evidence of carcinogenicity* in humans for non-Hodgkin lymphoma. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals. On the basis of tumours in mice, the United States Environmental Protection Agency (US EPA) originally classified glyphosate as *possibly carcinogenic to humans* (Group C) in 1985. After a re-evaluation of that mouse study, the US EPA changed its classification to *evidence of non-carcinogenicity in humans* (Group E) in 1991. The US EPA Scientific Advisory Panel noted that the re-evaluated glyphosate results were still significant using two statistical tests recommended in the IARC Preamble. The IARC Working Group that conducted the evaluation considered the significant findings from the US EPA report and several more recent positive results in concluding that there is *sufficient evidence of carcinogenicity* in experimental animals. Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby."

http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)70134-8/abstract

http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

Thanks,

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: February 6, 2014

SUBJECT: Glyphosate: Tier II Incident Report

PC Code: 103601, 103603, 103604, 103605, 103607, 103608, 103613, 417300
Decision No.: 487242
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA

MRID No.: NA

DP Barcode: D417808

Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 38641-94-0, 70393-85-0, 40465-66-5, 114370-14-8, 70901-12-1, 1071-83-6
40 CFR: NA

Ver.Apr.08

FROM: Shanna Recore, Industrial Hygienist
Carol Christensen, Epidemiologist
Elizabeth Evans, Environmental Protection Specialist
Khin Oo, MD, DABT, Environmental Health Scientist
Toxicology and Epidemiology Branch
Health Effect Division (7509P)

THROUGH: David J. Miller, Acting Chief
Toxicology and Epidemiology Branch
Health Effects Division (7509P)

06-FEB-2014

TO: Thomas Bloem, Risk Assessor
Risk Assessment Branch I
Health Effects Division (7509P)

SUMMARY

HED is currently re-evaluating the toxicity, exposure, and risk profile of glyphosate under the Food Quality Protection Act (FQPA)-mandated Registration Review program. The registration review program is designed to ensure EPA evaluates new information regarding pesticides on a 15 year cycle, and to update the risk assessment and initiate new regulatory requirements, when appropriate, to ensure the protection of human health and the environment. Pesticides included in

the registration review program are pesticides for which EPA completed a Re-registration Eligibility Decision (RED) under the FQPA.

One component of the Agency's Registration Review Program is consideration of acute and chronic health effects observed in the human population as a possible consequence of glyphosate exposure. Given the magnitude and frequency observed in the initial screening evaluation of acute poisoning incidents related to glyphosate use, HED determined that a more extensive Tier II report of the acute and chronic human health effects linked to glyphosate use should be performed. A Tier II report provides additional details and greater depth in scope of review information relating to human exposure. Information streams queried for this report include acute pesticide poisoning event (incident data) and surveillance data, medical case reports of human exposure to glyphosate, general medical information, biomonitoring data, and observational epidemiology studies. Utilization of these data will aid HED in better defining and characterizing the potential risk of glyphosate pesticide products to the U.S. population, and particular sub-groups such as workers and children.

A review of medical literature finds most of the accidental ingestions of glyphosate formulations resulted in mild symptoms such as irritation of oral and upper gastrointestinal mucosa and were self limited. However, intentional ingestions caused moderate to severe symptoms in multiple organs.

HED reviewed five pesticide incident data sources (IDS, NPIC, California PISP, NIOSH/SENSOR, and AAPCC). HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report, and the other databases and medical literature reviewed. These health effects primarily include dermal, ocular, and respiratory. HED did not identify any aberrant effects outside of those anticipated. While inconvenient for those who suffer adverse health effects, effects are generally mild/minor to moderate and resolve rapidly. The incident data available from IDS and NPIC suggest that homeowner mixing/loading/ applying (usually due to human errors and container leaks of glyphosate products) are responsible for almost half of the reported incidents. SENSOR-Pesticides incident data are consistent with IDS and NPIC, also suggesting that most reported incidents (50%) occur during application of glyphosate results. . However, the SENSOR-Pesticide incidents include both residential and occupational incidents. The incident data available from CA PISP suggests that occupational handling of equipment is responsible for most incidents due to equipment leaks and malfunction.

All of the databases showed a number of childrens' exposures (ranging from 5% to 27% of total cases). Based on the data in SENSOR, IDS, and NPIC, it appears that the childrens' exposures are due to primarily to postapplication exposure, accidental ingestion, and tampering with the product.

Ocular exposure and symptoms were reported in all of the databases, to both occupational and nonoccupational users, as a result of splash to the face or touching their eyes with the product on their hands. These symptoms primarily included eye irritation, redness, burning and blurred vision.

Trends over time data from IDS (2008 to 2012), PISP (2005 to 2010), SENSOR-Pesticides (1998 to 2009) and AAPCC (2001 to 2012) data were reviewed. Based on IDS and AAPCC, which are primarily non-occupational cases, incidents appear to be decreasing over time. CA PISP data represents both occupational and non-occupational incidents. This data appears to show incidents to be relatively steady over time. The SENSOR-Pesticide data also represent both occupational and non-occupational cases. For this data, occupational case reports involving glyphosate appeared to be increasing until 2008 and non-occupational case reports appear to be increasing over time. The increase in non-occupational case reports may be reflective of increased SENSOR state capacity to collect non-occupational pesticide surveillance data.

While HED identified several dozen glyphosate environmental epidemiology studies, few of these studies reflected an *a priori* research interest in the potential role of glyphosate and chronic disease outcomes, and most studies were hypothesis-generating in nature. Given this and other limitations of these studies, we cannot conclude glyphosate plays a role in any of the health outcomes studied across this epidemiologic database. EPA will continue to follow the literature concerning the potential role of the chemical in certain cancer and non-cancer outcomes, particularly respiratory health and lymphohematopoietic cancers such as non-Hodgkin lymphoma (NHL) and multiple myeloma (MM).

1. BACKGROUND

Glyphosate is a nonselective herbicide which acts via blocking the activity of the enzyme, 5-enolpyruvylshikimate 3-phosphate synthase (EPSPS). EPSPS is produced only by green plants and is involved in the synthesis of the amino acids tyrosine, tryptophan, and phenylalanine.

Glyphosate is registered for use on a variety of fruit, vegetable, and field crops as well as for aquatic and terrestrial uses. It is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Glyphosate was first registered for use by the United States Environmental Protection Agency (U.S. EPA) in 1974 and reregistration was completed in 1993. Glyphosate is among the most widely used pesticides by volume. It ranked eleventh among conventional pesticides used in the U.S. during 1990-91. In recent years, approximately 13 to 20 million acres were treated with 18.7 million pounds of glyphosate annually. The largest use sites include hay/pasture, soybeans and field corn (D362745, 06/03/2009, J. Langsdale et al.).

In March 2009, HED prepared a preliminary Tier I human incident review of glyphosate human incident reports by consulting the OPP Incident Data System (IDS) for reports of poisoning incidents. During the time period captured in the screening report, 2002 to March 2009, 289 incidents involved products containing the single active ingredient glyphosate. Based on the IDS, 8 major types of adverse health effects were identified: gastro-intestinal (4.8%), dermal (30.1%), upper-respiratory (10.3%), neurological (34.3%), cardiovascular (0.3%), ocular (13.8%), muscular (0.3%), and combination (5.5%) effects (*Updated Review of Glyphosate Incident Reports*, M. Hawkins and J. Cordova, 03/12/2009). Given the frequency and relative severity, HED determined it would further evaluate glyphosate acute poisoning event reporting and surveillance databases as well as a review of published literature as to the acute and chronic health effects associated with glyphosate exposure by performing a Tier II review.

It is important to recognize, however, that reports of adverse health effects allegedly due to a specific pesticide exposure (i.e., an "incident") are largely self-reported and therefore, generally speaking, neither exposure to a pesticide or reported symptoms (or the connection between the two) are validated. Therefore, only rarely can causation be determined or definitively identified based on incident data. However, incident information can provide important feedback to the Agency. Human incident data, in concert with other human observational studies (medical case reports, general medical information, biomonitoring and epidemiological studies) and the human health risk assessment, can assist the Agency in determining potential risks of pesticides/pesticide product exposure, and can help characterize that risk. This review assesses acute pesticide poisoning incidents, medical case reports, and published epidemiology studies to inform the preliminary risk assessment for glyphosate.

a. Tier II Overview

Historically, the Agency has relied on toxicity studies conducted on animals and exposure information measured or modeled in relevant populations regarding the pesticide's use pattern when considering the registration or re-registration of a pesticide. While the use of these data, models and standard exposure assumptions will likely not diminish, the relevance of human data that report acute and chronic health effects experienced in the population will continue to increase. Improved exposure assessment methods, use of biomarkers of disease as well as exposure, and continued merging of toxicology and epidemiology through adverse outcome pathway/MOA framework analysis and molecular epidemiology methods will enhance the utility of public health data as a stream of evidence in the risk assessment.

Tier I incident reports make recommendations on whether there is a need for a more in-depth Tier II analyses based on high frequency and/or severity of incidents in IDS, SENSOR-Pesticides, and the preliminary Agricultural Health Study results for a particular active ingredient. If a recommendation for further in-depth analyses (Tier II) is made, a broader set of available incident data sets are reviewed and a review of available epidemiological studies and

human toxicology and medical case reports is conducted. Trend analyses and summaries (root cause analysis) with respect to incidents is done, as well as additional analysis on a product-specific (as opposed to active ingredient) basis.

This Tier II glyphosate analysis includes human observation data from a variety of sources including:

- Human toxicological reviews and medical case reports from the literature,
- Human incident (poisoning) data from such sources as OPP's Incident Data System (IDS) database, NIOSH SENSOR, the Agency-sponsored National Pesticide Information Center (NPIC), California's Pesticide Incident Surveillance Program (PISP), American Association of Poison Control Centers (AAPCC) Annual Reports, and
- Epidemiological studies from the literature.

2. MEDICAL CASE REPORTS

a. Literature Search Methodology

While much animal toxicology data exist and have been evaluated by OPP during the glyphosate registration review process medical data involving pesticides provide another source of information to evaluate risks of glyphosate. Medical case reports evaluate particular patients and describe the symptoms, signs, diagnosis, treatment, and follow-ups. Medical case series are similar to case reports, but focus instead on multiple patients with similar exposure, treatment and/or symptoms/signs. Case reports and case series provide insight into the potential effects of pesticide exposure on humans. It is important to remember, however, that often the exposure scenarios associated with case reports and series are high dose (suicides, attempted suicides, or non-accidental ingestions) and are dissimilar in some ways to inadvertent exposures which tends to be at substantially lower doses and with different exposure routes. Nevertheless, examining these cases can be valuable in that they illustrate the effects of frankly toxic doses and allow observation of what may be important health consequences of high-dose exposure. Medical information on pesticides are found in many locations; however the Agency has relied on information from databases for the period from 1975 to the present, querying the National Library of Medicine (PubMed, TOXNET), Web of Knowledge, Google Scholar, as well as the CDC and ATSDR databases, to identify relevant pesticide medical information. Specifically, the Agency looked across the following databases for this assessment:

- PUB MED comprises more than 22 million citations for biomedical literature from MEDLINE, life science journals and online books.
- TOXNET consists of HSDB (Hazardous Substances Data Bank) which contains comprehensive peer-reviewed toxicology data for about 5,000 chemicals.

- ATSDR Case-Studies provide information regarding clinical findings, treatment and current knowledge regarding pesticides.

- Google Scholar is a search engine that indexes the full text of scholarly literature across an array of publishing formats and disciplines. It includes most peer-reviewed online journals of Europe and America's largest scholarly publishers.

The Agency is confident that considering the above sources captures the critical medical information concerning the human health effects of glyphosate. A medical literature search on glyphosate in Pub Med, Web of Knowledge and Google was performed, using the terms (or key concepts): *glyphosate toxicity*; *glyphosate, poisoning*; *glyphosate*, *symptoms*. One hundred and ninety nine citations were recovered but many of them were not related to the human health effects of glyphosate. From the title and abstract review, animal studies with glyphosate and studies regarding environmental effects of glyphosate were removed. A Google Advanced Search and the EPA library were used to retrieve full text articles. Thirty eight full text articles related to glyphosate and human health effects, toxicokinetics, toxicodynamics and case reports were reviewed.

b. Summary of glyphosate medical literature review.

Glyphosate [N-(phosphonomethyl)glycine] is a nonselective herbicide. Glyphosate inhibits the enzyme 5-enolpyruvyl-shikimic-3-phosphate-synthase in plants; however, mammals do not have this enzyme (Aaron, 2006). Glyphosate should thus possess low risk for mammalian toxicity. Glyphosate has been placed in Toxicity Category III for oral and dermal acute toxicity (i.e. oral LD_{50} 500 – 5,000 mg/kg), which means low acute toxicity for oral, and dermal exposures. It is a mild eye irritant and is not a dermal sensitizer. In addition, neurotoxicity was not observed in any of the acute, subchronic, chronic, developmental or reproductive animal studies performed with glyphosate (D398547, 11/14/2012, T. Bloem et al.).

However, glyphosate end products (commercial products) are usually formulated with different glyphosate salts with various concentrations of surfactant polyoxyethyleneamine (POEA) up to 50% and other ingredients (antifoaming agents, biocides and inorganic ions), rather than active ingredient glyphosate alone. For example, Roundup contains 41% glyphosate as the isopropylamine salt and 15% POEA. This can potentially make the end product more toxic than the active ingredient alone.

There have been many reports in the medical literature on acute poisoning with commercial glyphosate –based formulations. Most of the accidental ingestions of glyphosate formulations resulted in mild symptoms such as irritation of oral and upper gastrointestinal mucosa and were self limited. However, intentional ingestions caused moderate to severe symptoms in multiple organs. It was reported that most of these symptoms may actually be related to the surfactant polyoxyethyleneamine (POEA) or other ingredients in the commercial glyphosate formulations

(Bradberry, Proudfoot, & Vale, 2004; Sawada, Nagai, Ueyama, & Yamamoto, 1988). Since human poisoning with this herbicide is not with the active ingredient (glyphosate) alone but with various mixtures, it is not easy to identify the exact cause. Table A in Appendix 1 identifies various glyphosate product formulations that have been previously identified by the U.S. Forest Service (Diamond & Durkin, 2011).

Experimental studies have found that the toxicity of a surfactant (POEA) is greater than the toxicity of glyphosate alone (Bradberry et al., 2004; Peixoto, 2005). Hour B.T. et al. (2012) also reported that surfactants interfere with the proton gradient in the mitochondria wall, affecting energy production in cells leading to cell death. According to Peixoto F. (2005), Roundup interferes with electron transfer by partially inhibiting mitochondrial complexes II and III, leading to depressed ATPase activity. When the authors used the glyphosate alone in the same concentration they did not find this effect. Diamond (2011) mentioned that there were various concentrations of POEA surfactant, glyphosate salts and other ingredients in different glyphosate products and the resulting adverse health effects may be different. The adverse health effects of accidental and intentional exposures to glyphosate products are summarized from medical case reports in the following sections.

c. Summary of Case Reports

Various case reports are summarized in this section, and are divided into accidental/unintentional exposures and intentional exposures.

i. Accidental/Unintentional Exposures

Inhalation Exposure:

- Ptok M., (2009) reported that a 26-year-old school teacher suffered from a severe dysphonia (abnormal vocal sounds) a few hours after applying glyphosate product (more detailed information regarding the exposure was not available). She informed that she had followed the instructions on the product label. A laryngoscopy found decreased vocal fold mobility. The symptoms disappeared spontaneously and her vocal fold mobility returned to normal after 6 weeks (Ptok, 2009).
- A 42 year old worker exposed to Roundup suffered from burns in the mucosal lining of the pharynx and larynx and acute toxic pneumonitis (inflammation of lung tissue) (Pushnoy, Avnon, & Carel, 1998). He presented at the ER with shortness of breath, irritative cough, dizziness, discomfort in the throat and episodes of hemoptysis (blood in the sputum). According to the patient he developed these symptoms after cleaning the clogged sprayer containing Roundup inside a small room. His chest X-ray (Figure 1) showed extensive bilateral alveolar involvement. The authors stated that the surfactant

polyoxyethylene amine is the main reason for erosion of upper respiratory tract mucosal lining and lung tissue.

Figure 1. Chest radiograph

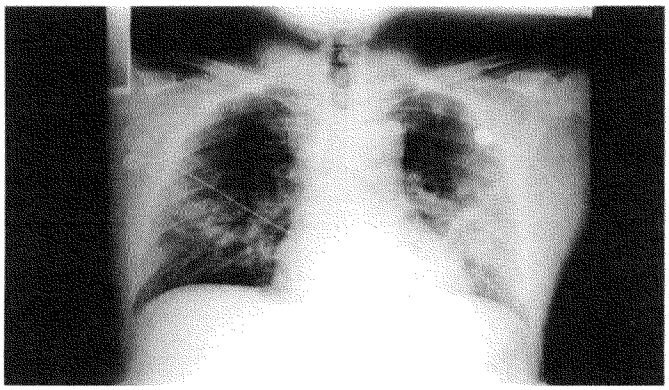


FIGURE 1. Chest radiograph on admission demonstrating interstitial bilateral infiltrations.

Dermal Exposure:

Although glyphosate alone has been found to have low dermal toxicity, there were several cases of severe dermal effects due to accidental exposure to formulations containing glyphosate and surfactants.

- Amerio et al. (2004) reported that a 78 year old woman presented with extensive chemical burns on her back, knees and legs caused by an accidental contact with a glyphosate-surfactant formulation (41% glyphosate and 15% POEA). She knelt on the ground where her son had just sprayed the herbicide. Later she put on clothing that had been lying on the same ground contaminated with the herbicide. At home, she lay down in the same clothing on the couch. After several hours she noticed burning sensation on areas that had been in touch with the glyphosate product; and sheets of necrotic epidermis (dead skin) had sloughed, causing extensive erosions. Fluid filled lesions (bullae) were also appeared on the dorsum of the feet. She was treated with normal saline wet dressing, petrolatum gauze, topical hydrocortisone 1% plus silver-sulfadiazine cream, and systemic antibiotic piperacilline/tazobactam (to prevent secondary infection). It took four weeks to heal these skin lesions. The authors mentioned that effects of glyphosate on human skin depend on several factors, such as concentration of glyphosate in the formulation, the duration of exposure, the presence of a surfactant in the formulation, and skin conditions such as moisture, sweat, and the presence of sebum (Amerio et al., 2004).

- Mariager et al. (2013) also described a 43-year old man with severe chemical burns following prolonged accidental exposure to the herbicide Roundup Bio (isopropylamine salt of glyphosate and surfactant POEA with the pH of 4.5-5). The contents accidentally

sprayed on the patient when he shook the bottle. He did not wash the exposed areas for more than 24 hours. The next day he developed local swelling, bullae and exuding wounds on his left hand, arm, upper arm and axilla regions. Soon it changed into second degree skin necrosis with detachment of the epidermis. In addition, he had touched his face with contaminated hands resulting in swelling of the area around the eye. After three months, nerve conduction studies showed reduced nerve conduction in distal axons on the medial, ulnar and radial nerves in the exposed hand. Hand X-ray done after 4 months revealed osteopenia of carpal bones. After 9 months, the patient regained near normal sensation but he had severe atrophy of the intrinsic muscles of the hand and loss of strength with decreased range of motion. All other skin lesions had healed with scarring and alopecia (hair loss), (Figures 2, 3 and 4) (Mariager, Madsen, Ebbehoj, Schmidt, & Juhl, 2013).

Figure 2: Atrophy of hand muscles resulting in deformity (Mariager TP., et al.)

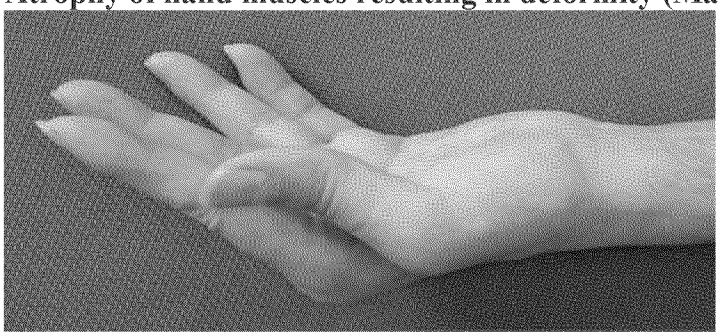


Figure 3: Osteopenia of the carpal bones (Mariager TP., et al.)

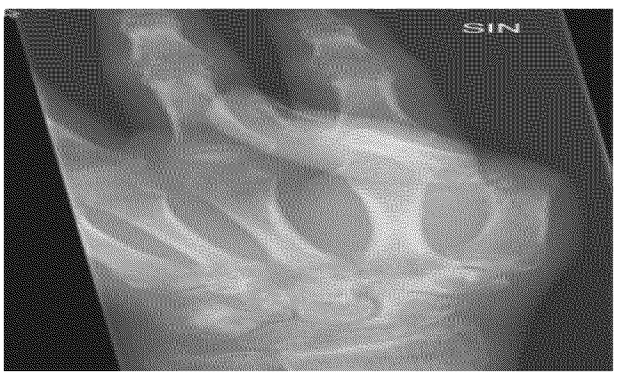
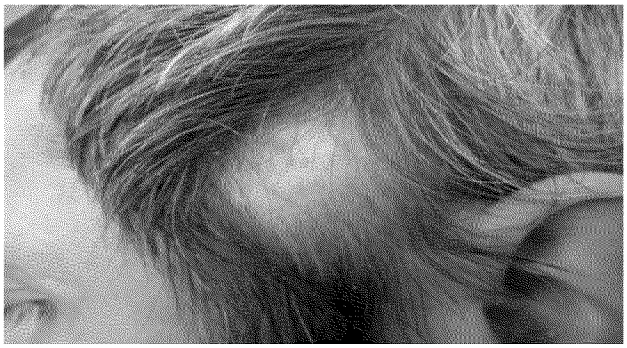
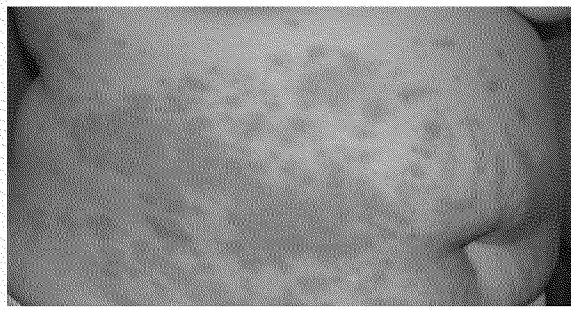


Figure 4: Chemical burn healing with alopecia (Mariager TP., et al.)



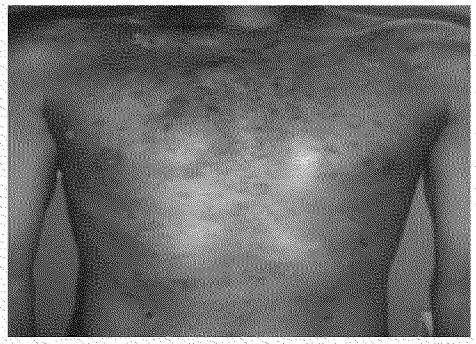
- Another dermal exposure involved a 37 year old female. She was exposed to glyphosate herbicide (Touchdown Premium) when the backpack containing the herbicide broke and wet her clothing. The herbicide contained 36% glyphosate ammonium salt which she diluted with water before using it. She admitted delaying in rinsing off the herbicide. At the end of the day she suffered from the irritant contact dermatitis, followed by erythemato-purpuric plaques developed on the upper extremities, on the abdomen, axilla and groin (Figure 5). The patient was treated with oral corticosteroids and antihistamines. The lesions got better in 2 weeks with post-inflammatory hyperpigmentation (Heras-Mendaza, Casado-Farinas, Paredes-Gascon, & Conde-Salazar, 2008).

Figure 5: Erythematous and purpuric plaques on the abdomen (Heras-Mendaza F., et al. 2008)



- Fisher KR., et al (2008) reported a patient who developed pemphigus vulgaris (PV) on his body and extremities, after an occupational exposure to fumes of burning empty glyphosate drums. PV is an autoimmune skin lesions characterized by bullae that rupture quickly and progress to crusted erosions. Authors mentioned that their patient had been using glyphosate product with 41% glyphosate isopropylamine salt on the farm for the past 3 years, which might have sensitized the skin (Figure 6) (Fisher et al., 2008).

Figure 6: Scattered bullae and vesicles on the body (Fisher KR., et al., 2008)



Accidental death with glyphosate trimesium formulation (Touchdown):

- Sorensen et al. (1999) reported an accidental ingestion of Touchdown causing the death of a 6-year-old boy. He accidentally ingested a mouthful of the herbicide and died within a couple of hours. His father had placed the bottle containing the herbicide on the table in the garage and the child mistook it for a drink. The child spat almost all of it out and swallowed only a small amount because of the bad taste. He then went into the house and drank some water. Soon he developed pain, vomiting, and then collapsed. The father performed cardiopulmonary resuscitation (CPR) when he noticed that his son was not breathing and had no pulse. The child was taken to the hospital and, in spite of the resuscitation attempt, he passed away. The post-mortem examination revealed edema of the mucus membranes of the airways, erosion of the mucus membranes of the gastrointestinal tract, pulmonary edema, cerebral edema, and dilated right atrium and ventricle of the heart (Sorensen & Gregersen, 1999).

ii. Intentional Exposures

Intentional exposure or suicide cases can assist in understanding the relative sensitivity of humans to the toxicity of glyphosate formulations. Some of the case reports may be used for estimating the acute lethal toxicity of glyphosate-surfactant formulations.

- Bradberry et al. (2004) reported that ingestion of >85 mL of the concentrated formulation can cause serious toxicity in adults. Pain in mouth, throat, stomach and dysphagia (difficulty in swallowing) due to gastrointestinal corrosion are common. In severe cases, pulmonary edema (fluid inside the lung), respiratory distress, cardiac arrhythmias (abnormal heart rhythm), shock, and impaired consciousness may occur. In addition, renal failure, metabolic acidosis and hyperkalemia (high serum potassium level) may take place requiring hemodialysis for treatment (Bradberry et al., 2004).

- Zouaoui et al. (2013) reviewed 13 cases of glyphosate herbicide intentional poisoning, and found that the most common symptoms were oropharyngeal ulcerations, nausea and vomiting. The main biochemical abnormality was lactic acidosis. Other adverse health effects were: respiratory distress; cardiac arrhythmia; hyperkalemia; impaired renal function; liver toxicity; and altered consciousness. In mild to moderate intoxications, blood glyphosate concentrations were in the range of (0.6 – 150) mg/L with a mean value of 61 mg/L. In the severe intoxication case, the blood glyphosate concentration was found at 838 mg/L; and in fatal cases the range of (690-7480) mg/L with a mean value of 4146 mg/L was found (Zouaoui, Dulaurent, Gaulier, Moesch, & Lachatre, 2013).

- Chang CY., et al., (1999) studied lesions in gastrointestinal tract of 50 patients with glyphosate-surfactant oral ingestion as a suicide attempt. They found that esophageal injury was seen in 68% of the patients (15% grade 1, 15% grade 2a and 4% grade 2b); gastric injury in 72% (22% grade 1 and 8% grade 2a), and duodenal injury in 16% (7% grade 1 and 1% grade 2a). [According to the Zargar's modified grading system, Grade 1 injuries have swelling and redness of mucosa. Grade 2a injuries have friability, hemorrhage, erosion, blistering, whitish membranes, exudates or superficial ulcerations. Grade 2b injuries have features of grade 2a plus circumferential ulcerations] (C. Y. Chang et al., 1999). Chen HH., et al., (2013) stated that patients with grade 2b esophageal injury suffered from a greater incidence of respiratory (100.0% versus 5.9%, $P = 0.001$) and gastrointestinal (66.7% versus 11.8%, $P = 0.034$) complications than patients with grade 1 injury (H. H. Chen et al., 2013).

- Talbot and Shiaw (1991) reviewed 93 cases of exposure to Roundup from 1980 to 1989. They found that the lethal cases had ingested glyphosate herbicide (41% solution), ranging from 85-200 mL. These patients had: erosion of gastrointestinal tract (66%); sore throat (43%); dysphagia (31%): and gastrointestinal hemorrhage (8%). Other organs involved were: non-specific leucocytosis in blood (65%); pulmonary edema (23%); liver dysfunction (19%); cardiovascular shock (18%); kidney dysfunction (14%); and central nervous system (changes in the level of consciousness) (12%) (Talbot et al., 1991).

- A case-control study conducted by Lee C.H. et al., (2008) and a retrospective study done by Lee H.L. et al., (2000) found similar multi-organ effects. Author's found that useful indicators for predicting serious outcome from commercial glyphosate product were: metabolic acidosis; hyperkalemia; respiratory distress requiring intubation; tachycardia; and elevated serum creatinine levels. According to authors, pulmonary toxicity and renal toxicity were mostly responsible for the fatality (C. H. Lee, Shih, Hsu, Hung, & Lin, 2008; H. L. Lee, Chen, Chi, Huang, & Tsai, 2000).

- Kamijo Y. et al. (2012) and Bando H. et al. (2010) reported that ingestion of Roundup Maxload (48% glyphosate potassium salt) can cause severe hyperkalemia and severe complications (Bando et al., 2010; Kamijo, Mekari, Yoshimura, Kan'o, & Soma, 2012). A 69- year old female had serum potassium levels of 10.7 mEq/L (normal range is 3.5 – 5 mEq/L), loss of consciousness, low blood pressure, metabolic acidosis and abnormal cardiac rhythm (ventricular tachycardia) after ingesting about 500 mL of Roundup Maxload. Serum glyphosate levels on admission and after 20 hours were 1625.74 and 100.44 µg/mL, respectively. Chest X-rays showed diffuse pulmonary infiltrate. The endoscopy showed pharyngeal edema, esophageal erosions, and gastric erosions. Patient was given activated charcoal and put on cardiopulmonary support, continuous hemodialysis, and mechanical ventilation. Although the patient recovered, the authors reminded that glyphosate products containing high potassium that can be easily purchased in retail stores possess a serious problem in Japan.

- Stella J. and Ryan M. (2004) stated that the triad of pulmonary edema, metabolic acidosis, and hyperkalemia indicates a poor outcome, and may not respond to even the most intensive supportive care (Stella & Ryan, 2004).

- Chang CB., et al. (2009) also reported that a 57-year old woman who ingested 400 ml of a Taiwanese glyphosate formulation (41% glyphosate isopropylamine and 15% polyoxyethyleneamine) died in spite of intensive treatment. On admission to the hospital, the patient was drowsy although vital signs were within the normal range. Shock and respiratory failure developed within 5 hours after admission to the hospital. She was transferred to the intensive care unit, put on the mechanical ventilator, and treated according to the critical care procedures. The hyperkalemia was corrected with insulin/glucose infusion and oral kayexalate. The acidosis was corrected by intermittent sodium bicarbonate infusions. However, refractory shock persisted despite the administration of fluids, dopamine, vasopressin, epinephrine, and norepinephrine. Ventricular tachycardia developed on the third day of admission and the patient died (C. B. Chang & Chang, 2009).

- Although animal studies found that absorption of glyphosate from the stomach is inefficient, Roberts DM., et al. (2010) stated that in humans, commercial glyphosate solution is rapidly absorbed from the GI tract, and followed first-order elimination with a half-life ranged from (2.7-3.6) hours. This reflects the rapid development of adverse health effects in humans (Roberts et al., 2010).

- Sribanditmongkol P., et al. (2012) reviewed the pathological and toxicological results of a fatal poisoning case. The postmortem examination of a 37-year old woman who ingested 500 mL of concentrated Roundup formulation (41% glyphosate as the

isopropylamine salt and 15% polyoxyethylene amine) revealed hemorrhagic areas in the gastric mucosa and marked dilatation and thin walls in the small intestines. A mild degree of pulmonary congestion and edema was observed in both lungs. The glyphosate level in the serum was 3.05 mg/mL; the glyphosate level in the gastric contents was 59.72 mg/mL (Sribanditmongkol, Jutavijittum, Pongraveevongsa, Wunnapuk, & Durongkadech, 2012).

- According to Wu J.Y. (2006), intravenous injection of 250 mL of diluted glyphosate (150 mL of glyphosate in 500 mL of water) in a suicide attempt caused acute hemolysis (rupturing red blood cells inside the blood vessels) in a 22-year-old male patient (Wu, Chang, Tseng, Deng, & Lee, 2006).

iii. Direct Renal Toxicity

- Yoo et al. (2009) found that the product (41% glyphosate with surfactant) can cause direct toxic effects on kidneys. Their patient had suffered from the severe tubulointerstitial nephritis without the cardiovascular collapse which means that the renal insufficiency in this case was not secondary to the low blood pressure and poor renal perfusion, but due to direct toxic effect of glyphosate product on kidneys. He was admitted to the hospital 30 minutes after ingesting 90 mL of glyphosate herbicide. On arrival, his serum creatinine was normal (0.8 mg/dL) and other laboratory findings including liver, cardiac, and muscle enzymes were within normal ranges. Two days after admission, although his vital signs were stable, his serum creatinine abruptly increased to 8.2 mg/dL and oliguria (very low urine output due to renal insufficiency) developed. The kidney biopsy also showed the chemical/glyphosate-induced nephrotoxic injury. He was treated with hemodialysis and two weeks later, his renal function started to improve slowly (Yoo & BS., 2010).

iv. Neurotoxicity

Although neurotoxicity was not observed in any of the acute, subchronic, chronic, developmental or reproductive animal studies performed with the glyphosate, there were few case reports with central nervous system effects suggesting direct neuronal toxic effects from the glyphosate-surfactant herbicide (GlySH).

- Malhotra et al. (2010) reported that a 71-year-old male who attempted suicide with the commercial glyphosate formulation developed a prolonged (>7days) but reversible encephalopathy. He also had cardiogenic shock and severe metabolic acidosis (pH 7.13; HCO_3 13.2 mmol/L). His blood acetylcholinesterase level was within normal range. Authors mentioned that although glyphosate has a carbon and phosphorus moiety it does not inhibit acetylcholinesterase enzyme unlike organophosphate pesticides. The EEG (electroencephalogram) indicated encephalopathy. He was treated in the intensive care

unit and also received hemodialysis. He fully recovered after 15 days in the hospital (Malhotra, Ghia, Cordato, & Beran, 2010).

- A case of aseptic meningitis after ingestion of about 150 mL of commercial glyphosate herbicide (41% glyphosate and 15% polyoxyethyleneamine) was reported by Sato C et al. (2011). A 58 year-old female presented with signs and symptoms of meningitis such as neck stiffness, rigidity of limbs, Kernig's sign (severe stiffness of the hamstring muscle causing an inability to straighten the leg when the hip is flexed to 90 degrees), and altered consciousness. All bacteriological and virological tests were negative. Glyphosate level in the cerebrospinal fluid (CSF) was 122.5 μg/ml. Authors mentioned that signs and symptoms of meningitis decreased as the concentration of glyphosate in CSF decreased. She completely recovered after 39 days due to the aggressive supportive care in the intensive care unit. The authors determined that the findings were suggestive of aseptic meningitis caused by the commercial glyphosate poisoning (Sato, Kamijo, Yoshimura, & Ide, 2011).

- Potrebic et al. (2009) described the neurologic lesion of a 56-year old woman who ingested about 500 mL of herbicide containing glyphosate isopropylamine salt. She suffered from hypotension, hyperkalemia, respiratory and renal failure and fell into a coma. Although the patient received the intensive care, she did not regain consciousness. An MRI revealed bilateral extensive white matter lesions of the brain stem and Pons (Potrebic, Jovic-Stosic, Vucinic, Tadic, & Radulac, 2009).

- Wang G., et al (2011) reported that a previously healthy 44 year-old woman presented with rigidity, slowness and resting tremor (typical of Parkinsonism) in all four limbs. She had worked exclusively at the glyphosate production division for 3 years while wearing only basic personal protective equipment (PPE) (gloves or face mask) for 50 hours a week. The MRI revealed bilateral hypotense lesions in the globus pallidus, the substantia nigra, and in the cerebral peduncle of the brain. Authors stated that the patient's occupational history and MRI results indicated a secondary Parkinsonism due to glyphosate product, rather that primary idiopathic Parkinson's disease (G. Wang, Fan, Tan, Cheng, & Chen, 2011).

v. Determination of blood glyphosate level and urine level of metabolite

Serum glyphosate and its metabolite aminomethyl phosphonic acid (AMPA) in urine can be determined by gas chromatography-mass spectrometry (GC-MS) (Hori, Fujisawa, Shimada, & Hirose, 2003; Motojyuku et al., 2008). Wang Y., et al., 2012 reported that ion chromatography is a simple, sensitive and accurate method to prove that the patient had a glyphosate poisoning (Y. Wang, Wu, Lian, & Shi, 2012).

d. Conclusion

Although animal studies showed glyphosate to have limited toxicity, medical case reports suggest that glyphosate end use products (formulated with, different types of glyphosate salts and various concentrations of surfactants and adjuvants), may be more toxic than the active ingredient alone. Since human poisoning reviewed were not with the active ingredient (glyphosate) alone but with various mixtures, it is not easy to identify the exact cause. Nevertheless, the medical literature reviewed indicates that most of the accidental ingestions of glyphosate formulations resulted in mild symptoms such as irritation of oral and upper gastrointestinal mucosa and were self limited. However, intentional ingestions caused moderate to severe symptoms in multiple organs.

3. HUMAN INCIDENT DATA

As indicated above, incident information can provide important feedback to the Agency, assisting in determining actual real-world exposures and risks posed by pesticides/pesticide products. Incident data are collected systematically, but differently, across the different databases used by the Agency with respect to such issues as coverage, certainty/confidence, fields/parameters reported, and usability. The aforementioned five pesticide incident data sources (IDS, NPIC, AAPCC, California PISP, and NIOSH/SENSOR) were used in this glyphosate report since they provide useful content and historical perspective. Various other comparable sources of data are available (e.g. the Bureau of Labor Statistics, emergency room outpatient surveillance, National Poison Data System (NPDS), etc.) but are not included in this review. By looking across the five data sources which were used, the Agency is confident that we are considering adequate and appropriate information to discern trends and patterns in glyphosate-associated acute pesticide poisonings, or "incidents."

a. OPP Incident Data System (IDS) (2008-2013)

The OPP IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6 (a) (2) reports from registrants and reports from other federal and state health and environmental agencies and individual consumers. Since 1992, OPP has compiled these reports in IDS. IDS contain reports from across the U.S. and most incidents contained in the system have all relevant product information recorded. Case reports or "narratives" are provided for each incident, with varying levels of detail; however, there is no effort at validating or assessing how likely it is that the reported exposure is causally related to the reported outcome. Because IDS has such extensive coverage, it is useful for providing temporal trend and geographic pattern information. The system is also useful for determining whether risk mitigation has helped reduce potential pesticide exposure through a decreased number of reported incidents.

For this evaluation, the OPP IDS was utilized for pesticide incident data on the active ingredient glyphosate (PC Codes 103601, 103603, 103604, 103605, 103607, 103608, 103613, and 417300). The incident data system records incidents in one of two modules: Main IDS and Aggregate IDS. Main IDS contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics. This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one active ingredient (as opposed to pesticide products with multiple active ingredients) are considered to provide more certain information about the potential effects of exposure from the pesticide. The higher severity outcomes include:

- H-A (death): If the person died;
- H-B (major): If the person alleged or exhibited symptoms which may have been life-threatening, or resulted in adverse reproductive effects or in residual disability; and
- H-C (moderate): If the person alleged or exhibited symptoms more pronounced, more prolonged or of a more systemic nature than minor symptoms, usually some form of treatment of the person would have been indicated, symptoms were not life threatening and the person has returned to his/her pre-exposure state of health with no additional residual disability.

Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries. The less severe human incidents include:

- H-D (minor): If the person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involve skin, eye or respiratory irritation; and
- H-E/H (unknown or no effects): If symptoms are unknown, unspecified or are alleged to be of a delayed or chronic nature that may appear in the future.

For the Main IDS, from January 1, 2008 to September 11, 2013, there are 502 cases reported that involve the active ingredient glyphosate. Of these 502 cases, there are 212 cases reported for the single chemical glyphosate in the database that occurred in the United States.[1] Summaries of these incidents are recorded in Appendix A. There was one death due to suicide, 6 suicide attempts, 2 suspected suicide attempts, and three malicious intent incidents which were not reviewed further for symptoms and are not included in the severity totals. There were also two incidents reported as lawsuits to IDS that were not considered in this report.

In addition to the suicide, there were two deaths reported. Upon further review these two reported deaths cannot be substantiated as being related to glyphosate. In one case, the death

[1] There were 16 events reported that occurred outside of the United States (5-Canada, 5-Brazil, 2-Argentina, 1-United Kingdom, 1-Jamaica, 1-Malawi, 1-Mozambique) that were not reviewed. Foreign incidents are not reviewed in detail because of the potential differences in the exposure patterns, use practices, and product formulation.

was reported by a third party with no further details. In the other case, a woman reported her husband and a neighbor both died of tumors. She reports that both she (major severity) and her husband (death) were exposed to Roundup three years before, and both developed tumors; however, the exposure to Roundup is unclear in the incident report.

One hundred and ninety nine cases were reviewed further for severity, exposure scenario, and reported symptoms. Nine of these incidents classified as majors; 185 incidents were classified as moderates; 2 incidents were classified as minor and 1 was classified as no effects. [2] The nine major severity incidents mostly involved applicators (4 were home owner mixer/loader/applicator and 2 were applicators (unknown if home or agricultural), 1 is nonagricultural occupational exposure and 2 are unknown exposure scenario.

Homeowner mixing/loading and/or applying resulted in the most (46%) reported exposures (most of these incidents occurred due to leaks, spills, splashes, mist and product blowback during mixing loading or applying (n=46), or equipment malfunction (n=12)) followed by post application exposure (14%). There were 9 exposures to children ages 11 years old and younger. These children were exposed through post application exposure or due tampering with the product, or accidental exposure. A summary the exposure scenario counts reported to Main IDS is provided in Table 1. The incident narratives for these incidents are provided in Appendix 2.

Table 1. Exposure Scenario Frequency of incidents reported to Main IDS (2008-2013)

Exposure Scenario	Number of reported incidents (%)
Home owner mixer/loader/applicator	90 (46)
Post application exposure	27 (14)
Unknown	20 (10)
Applicator exposure (unknown if homeowner of occupational)	17 (9)
Drift	12 (6)
Child exposures	9 (5)
Occupational application exposure	6 (3)
Accidental ingestions (adult)	5 (3)
Dermal contact (not applying)	4 (2)
Ingestion of treated fruit	2 (1)
Occupational mixing/loading	2 (1)
Non-agricultural occupational exposure	1 (0.5)
Smoked product in marijuana	1 (0.5)
Indoor use	1 (0.5)
Total	197[a]
[a]This total does not include the two death incidents which are described above.	

[2] Minor severity incidents and "no effects" incidents are typically reported to the Aggregate IDS, but do occasionally get reported to the Main IDS. For glyphosate, there are 6054 more minor severity incidents and 89 incidents with no or unknown effects reported to Aggregate IDS.

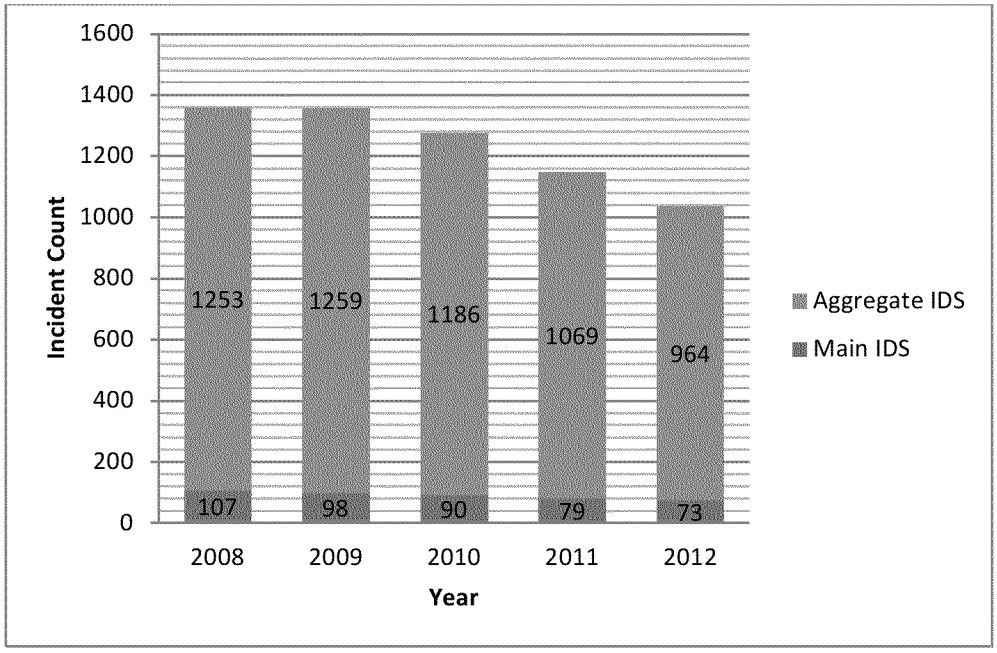
Based on the IDS reports, symptoms most often reported were dermal (n=72), neurological (n=70), respiratory (n=37), ocular (n=27), gastrointestinal (n=24), and cardiovascular (n=7). Note that a patient could exhibit multiple symptoms. Dermal symptoms reported include hives, swelling, rash, burning sensation, blotches, redness, peeling skin, and itchiness. Neurological symptoms reported include shaking, muscle cramps, diaphoresis, headaches, paresthesia, ataxia, disorientation, and dizziness. Respiratory symptoms reported included wheezing, coughing, sinus infection, nasal discharge, sore throat, and shortness of breath. Ocular symptoms reported were burning eyes, eye irritation and swelling, eye redness, foreign body sensation and vision problems. Gastrointestinal symptoms reported were nausea, diarrhea, vomiting, and abdominal pain. Cardiovascular symptoms reported include low blood pressure, chest tightness, chest pain, and heart attack.

In Aggregate IDS, queried from January 1, 2008 to May 8, 2013, there are 6143 incidents involving glyphosate. Because it falls within the categories reported as counts (which includes minor, unknown or no effects), there is no unique report that provides details about the incident and single chemical incidents are not distinguished from multiple chemical incidents; however, in general a high frequency of incidents indicates there is a high potential for exposure or elevated acute toxicity and vice versa.

Most (92%) of the incidents reported to IDS involving glyphosate were either minor severity (n=6054) or no or unknown effects (n=89). For the minor incidents, this means that a person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involved skin, eye or respiratory irritation. For the no/unknown effects, this mean that symptoms are unknown, unspecified or are alleged to be of delayed or chronic nature that may appear in the future.

The glyphosate incidents trend over time, from 2008 to 2012, was reviewed. The number of reported incidents appears to have decreased since 2008 (Figure 7).

Figure 7. Number of Glyphosate Incident per Year (2008 to 2012) Reported to IDS



The most often implicated glyphosate products in Main IDS are:

- Honcho Herbicide (Reg. No. 524-445) (n=88)
- Roundup Weed & Grass Killer Ready-To-Use Poison Ivy and Tough Brush Killer (Reg. No. 71995-23) (n=20)
- Roundup Weed & Grass Killer Ready-To-Use (Reg. No. 71995-32) (n=19).

In Aggregate IDS the main often implicated products are:

- Roundup Weed & Grass Killer Ready-To-Use Plus (Reg No. 71995-33) (n=1397)
- Roundup Weed & Grass Killer Concentrate Plus (Reg. No. 71995-29) (n=746)
- Roundup Herbicide (Reg. No. 524-445) (n=628)
- Roundup Weed & Grass Killer Ready-To-Use Poison Ivy and Tough Brush Killer (Reg. No. 71995-23) (n=390), and
- Roundup Weed & Grass Killer Ready-To-Use (Reg. No. 71995-32) (n=341).

Roundup Weed & Grass Killer Ready-To-Use Plus (Reg No. 71995-33) was implicated the most often in IDS (n=1397). This product is used to kill weeds and grasses in places, such as on patios, walkways, and driveways, (gravel, or mulch beds) in flower beds and vegetable gardens, around shrubs and trees, along fences and foundations. This is likely due to the high volume of use of this product. All the resulting incidents are minor severity.

b. National Pesticide Information Center (NPIC) (2007-2013)

The National Pesticide Information Center or NPIC is a cooperative effort between Oregon State University and EPA which is funded by EPA to serve as a source of objective, science-based pesticide information and respond to inquiries from the public and to incidents. NPIC functions nationally during weekday business hours through a toll-free telephone number in addition to the internet (www.npic.orst.edu) and email. Similar to Poison Control Centers, NPIC's primary purpose is not to collect incident data, but rather to provide information to inquirers on a wide range of pesticide topics, and direct callers for pesticide incident investigation and emergency treatment. Nevertheless NPIC does collect information about incidents (approximately 4000 incidents per year) from inquirers and records that information in a database. NPIC is a source of national incident information but generally receives fewer reports than IDS. Regardless, if a high frequency is observed in IDS, NPIC provides an additional source of information to see whether there is evidence of consistency across national data sets or possibly duplication and additional information about the same incident(s).

From 2007 to July 2013, 173 glyphosate incidents were reported to NPIC. NPIC estimates a certainty index as to whether an incident (including reported symptoms) was either definitely, probably, possibly, or unlikely to have been caused by the reported exposure to a pesticide, or whether the incident was unrelated to pesticides or if the incident was unclassifiable. Of the 173 reported incidents, 34 were reported as symptomatic and classified as definitely, probably, or possibly related to the glyphosate exposure and 55 cases were unclassifiable. Of these 55 unclassifiable cases, 53 were asymptomatic and 2 were reported as unknown symptoms. Of the 173 reported incidents, 82 were classified by NPIC as unlikely to have been caused by glyphosate. There were two suicide attempts which were not further reviewed. The Agency further reviewed the 89 incidents that were classified as definite, probable, possible and unclassifiable.

Of the 89 reported incidents reviewed by the Agency, homeowner mixing/loading and/or applying resulted in the most (n=42) reported exposures. Of these 42 exposures, most (n=26) occurred due to leaks, spills, splashes and product blowback during mixing loading or applying, or (n=11) equipment malfunction. Of the 89 reviewed incidents, the next most reported exposures were due to childrens exposures and drift (both 19%). A summary of the exposure scenario counts reported to NPIC is provided in Table 2.

Table 2. Exposure Scenario Frequency of Incident Reported to NPIC (2007-2013)

Exposure Scenario	Number of reported incidents (%)
Home owner mixer/loader/applicator	42 (47%)
Child exposures	15 (19%)
Drift	15 (19%)
Dermal contact (not applying)	6 (7%)
Occupational applicator	4 (4%)
Homeowner post application exposure	3 (3%)
Adult accidental ingestion	2 (2%)
Ate treated food from garden	1 (1%)
Unknown exposure	1 (1%)
Total	89

The symptoms most often reported to NPIC were respiratory (n=11), ocular (n=11), neurological (n=9), dermal (n=8), and gastrointestinal (n=5). Note that a patient could exhibit multiple symptoms. Respiratory symptoms reported included difficulty breathing, nasal discharge, nose irritation, and throat irritation. Ocular symptoms reported were red and irritated eyes, burning eyes, stinging eyes, blurry vision. Neurological symptoms reported include headaches, loss of balance, altered taste, dizziness, and Paresthesia. Dermal symptoms reported include rash, burning sensation, and redness. Gastrointestinal symptoms reported were nausea, diarrhea, and vomiting.

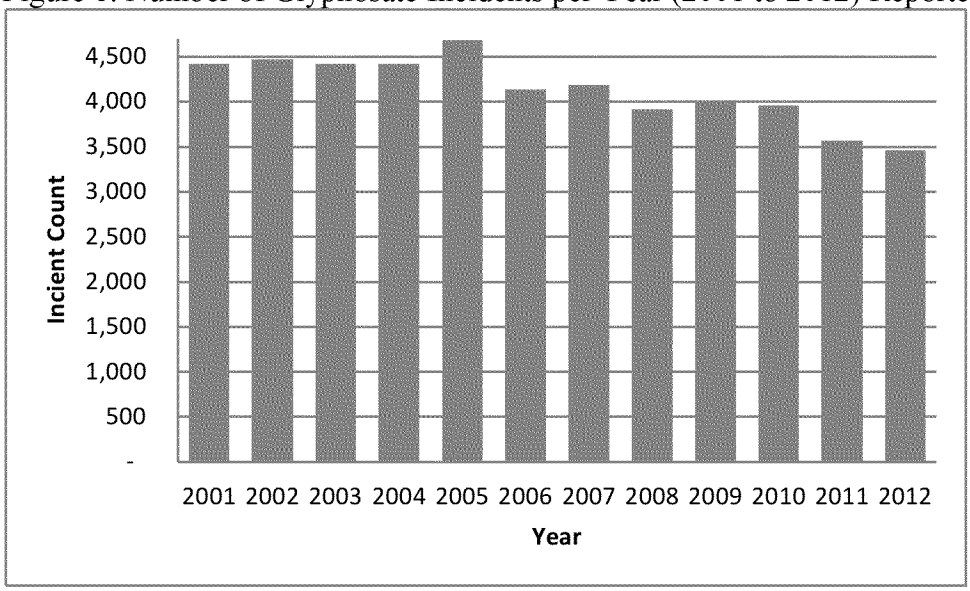
c. American Association of Poison Control Centers (2001-2012)

The American Association of Poison Control Centers (AAPCC) is a non-profit, national organization founded in 1958 that represents the poison control centers of the United States and the interests of poison prevention and treatment of poisoning. All of the calls to a poison control center are managed by a medical professional trained to answer questions about poisons. Additionally, AAPCC reports provide clearly summarized information on pesticide incidents within the context of other poisoning events.

AAPCC produces an annual summary report giving statistics and information on all the poisonings reported to PCCs in a calendar year (http://www.aapcc.org/annual-reports/). Glyphosate is included in the AAPCC annual summary and Agency examined the data from 2001 to 2012. According to the AAPCC 2012 annual report, glyphosate products ranked first with 3,464 single exposures among the reported human herbicide exposures (total reported herbicide exposures were 4717). There were 3257 unintentional exposures, and 875 cases were

to children 5 years old and younger.[3] A review of the AAPCC incident trend for glyphosate from 2001 to 2012 suggests a decrease in reported glyphosate incidents from 2005 to present (Figure 8).

Figure 8. Number of Glyphosate Incidents per Year (2001 to 2012) Reported to AAPCC



d. California Pesticide Illness Surveillance Program (PISP) (2005-2010)

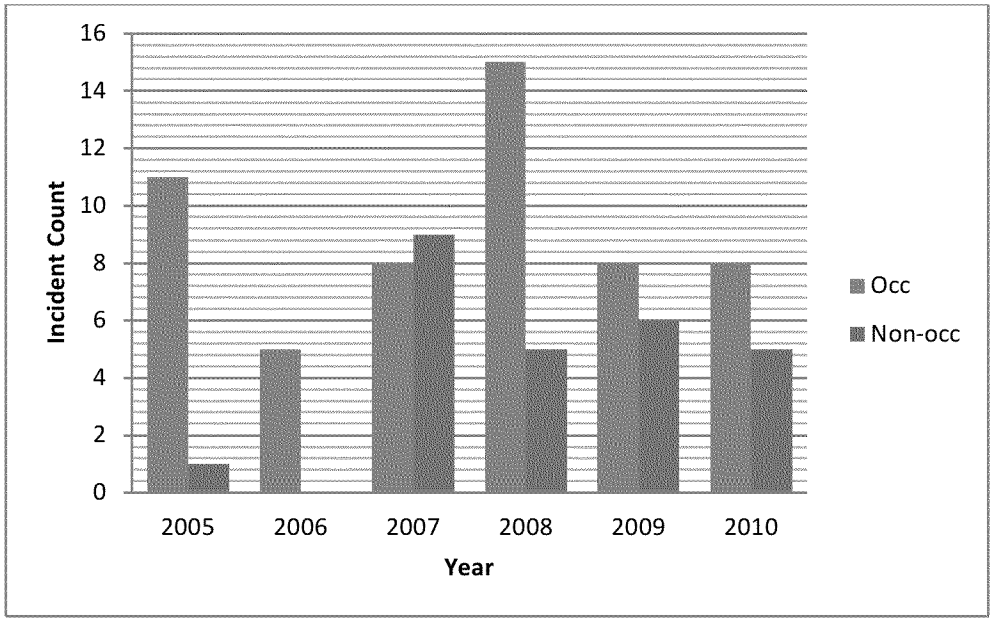
The California Pesticide Illness Surveillance Program (PISP) maintains a database of pesticide-related illnesses and injuries. Case reports are received from physicians and via workers' compensation records. The local County Agricultural Commissioner investigates circumstances of exposure. Medical records and investigative findings are then evaluated by DPR technical experts and entered into an illness registry.

PISP contains both residential and occupational pesticide incidents. PISP has limited coverage (only California) and is not particularly useful for trend over time information. However, the incident information is entered by professionals with expertise in pesticides, with extensive follow-up on each reported case so there is a high level of confidence in the information provided for each reported incident.

Eighty one cases were reported to PISP between 2005 and 2010 that involve the single reported active ingredient, glyphosate. All of these cases were classified as having a definite, probable or possible relationship with glyphosate. A total of 55 were occupational cases and 26 were non-occupational cases (Figure 9). The majority of cases (both occupational and non-occupational) occurred in a non-agricultural setting (N=56) such as landscaping or residential; 24 cases occurred in agricultural settings and in one case setting was unknown.

[3] 2012 Annual Report of the American Association of Poison Control Centers ' National Poison Data System (NPDS): 30th Annual Report
https://aapcc.s3.amazonaws.com/pdfs/annual_reports/2012_NPDS_Annual_Report.pdf

Figure 9. Number of Glyphosate Incidents per Year (2005 to 2010) Reported to PISP



The glyphosate exposure scenarios in PISP were as follows:

- 31 cases were related to the handling of application equipment, including:
    - 18 cases were related to application equipment leaks or malfunctions
    - Nine cases were related to problems while loading equipment or over-pressurizing equipment
    - Four cases involved the cleaning or repair of application equipment
    - Of these 31 equipment handling exposures, 22 cases were sprayed or splashed in the eyes or face while working with the application equipment. Eight of these cases were product handlers who were either failed to wear protective eyewear or removed their protective eyewear to load or repair the pressurized equipment and were splashed in the face and eyes (other cases may have had similar PPE issues but were not specifically cited in the report).
- Eight cases were the result of either drift (worker or bystander) or an application made while windy (exposing the handler)
- Nine cases were due to the ingestion of the product, five of which were accidental and four were intentional

- Five cases resulted from various accidents, such as vehicle problems
- Three cases involved toddlers who found the product and sprayed themselves
- Ten cases involved other various occupational exposure circumstances
- Eight cases involved other various bystander exposure circumstances
- Four cases involved other various homeowner exposure circumstances
- Three cases had unknown or unclear exposure scenarios

Symptoms Reported

Note that a patient could exhibit multiple symptoms. The most commonly reported symptom was eye irritation (n=39), followed by dermal irritation (n=37). Fourteen cases reported gastrointestinal symptoms, including vomiting, nausea, and diarrhea. Eleven cases reported respiratory symptoms including cough, wheeze, and shortness of breath. Nine cases reported a neurological symptom including headache, anxiety and dizziness. One case reported cardiovascular symptoms (Table 3).

Table 3. PISP 2005-2010: Health Effects for Glyphosate Cases

Health Effect*	Frequency
Ocular	39
Dermal	37
Gastrointestinal	14
Respiratory	11
Neurological	9
Cardiovascular	1
* Cases may report multiple health effects	

The most notable exposure pattern in the PISP data is the splashes to the eye/face during equipment handling. Appropriate PPE use, particularly protective eyewear, and equipment pressurization were important contributing factors for the glyphosate incident reports in PISP.

e. SENSOR-Pesticides (1998-2009)

The SENSOR-Pesticides database covers 11 states from 1998-2009, although reporting varies from state to state. Cases of pesticide-related illnesses are ascertained from a variety of sources, including: reports from local Poison Control Centers, state Department of Labor workers' compensation claims when reported by physicians, reports from State Departments of Agriculture, and physician reports to state Departments of Health. Although both occupational and non-occupational incidents are included in the database, SENSOR focuses on occupational pesticide incidents, and is of particular value in providing that information. A state SENSOR contact specialist attempts to follow-up with cases and obtains medical records to verify symptoms, circumstances surrounding the exposure, severity, and outcome. Using standardized protocol and case definitions derived from poison center reporting, SENSOR coordinators at State Departments of Health enter the incident interview description provided by the case, medical report, physician and patient into the SENSOR data system. The SENSOR data system is accessible to participating states and EPA.

A query of SENSOR-Pesticides 1998-2009 finds a total of 834 case reports involving glyphosate (pc codes 103601, 103603, 103604, 103605, 103607, 103608, 103613, 417300); of these, 505 involve a single active ingredient (ai). The 505 single ai cases, stemming from 495 events (no large multiple exposure events were identified), will be reviewed for this analysis. Six cases were high in severity, 57 were moderate in severity and 442 were low in severity (Table 4). Case narratives for all high and moderate severity cases are provided in Appendix 3.

Table 4. SENSOR-Pesticides 1998-2009 Glyphosate Cases by Severity (N=505)

Severity	Incident Count
Fatal	0
High	6
Moderate	57
Low	442
Total	505

Occupational and Nonoccupational[4]

- 272 cases were work-related
- 186 cases were not work-related
- 47 cases were unknown/unclear

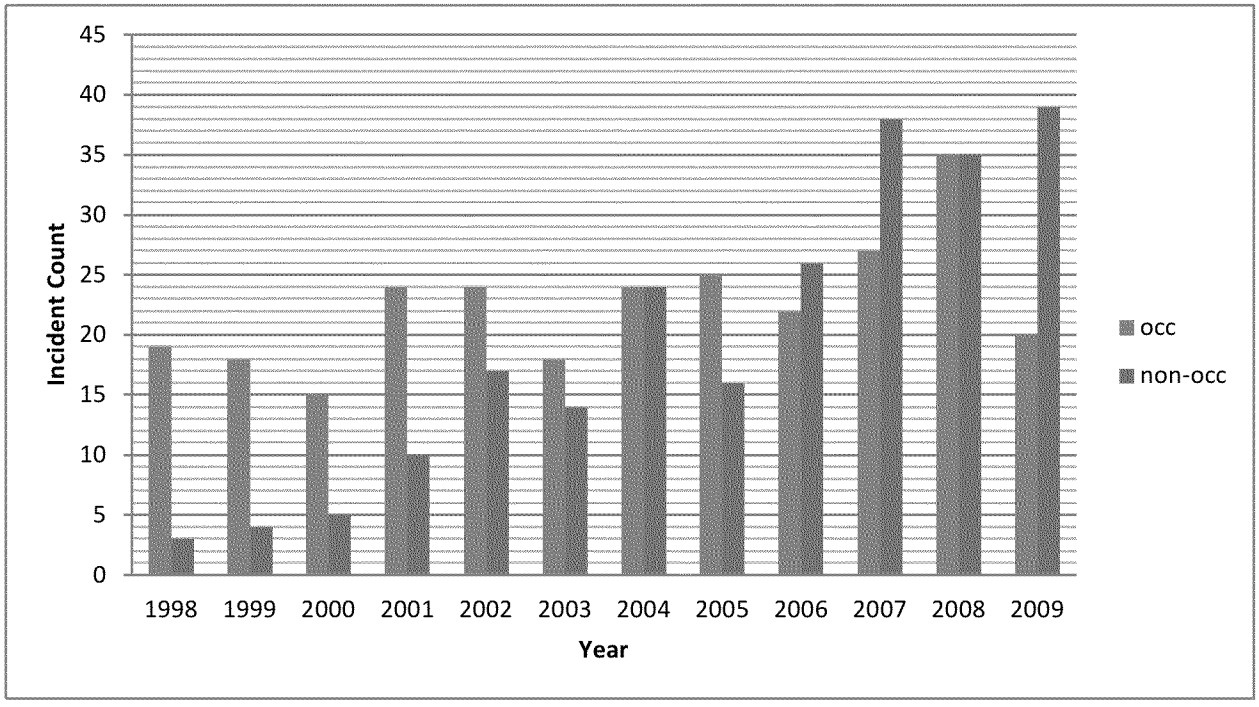
[4] SENSOR-Pesticides defines work-related cases as those illness and injuries occurring at the case's place of work.

Overall, occupational case reports involving glyphosate appeared to be increasing until 2008 and non-occupational case reports appear to be increasing over time. This trend is shown in Table 5 and the corresponding Figure 10, broken down by occupational and non-occupational case reports. The increase in non-occupational case reports may be reflective of increased SENSOR state capacity to collect non-occupational pesticide surveillance data.

Table 5. SENSOR Glyphosate Incident Count per Year (1998-2009)

Year	Occupational	Non-Occupational/ Unknown	Total
1998	19	3	22
1999	18	4	22
2000	15	5	20
2001	24	10	34
2002	24	17	41
2003	18	14	32
2004	24	24	48
2005	25	16	41
2006	22	26	48
2007	27	38	65
2008	35	35	70
2009	20	39	59
Year blank	1	2	3
Grand Total	**272**	**233**	**505**

Figure 10. Number of Glyphosate Incident per Year (1998 to 2009) Reported to SENSOR-Pesticides



Reported Symptoms

Dermal symptoms were most frequently reported (n=244) followed by ocular symptoms (n=194). The breakdown of all the symptoms are included in Table 6.

Table 6. SENSOR-Pesticides 1998-2009: Reported Health Effects for Glyphosate Cases

Health Effect*	Frequency
Dermal	244
Ocular	194
Nervous System	160
Gastrointestinal	157
Respiratory	148
Miscellaneous	48
Cardiovascular	23
Renal	5
* Cases may report multiple health effects	

Route of Exposure*
Dermal-244
Inhalation-150
Ingestion-57
Ocular-156
Unknown-32
*Case may have been exposed via multiple routes.

Multiple Exposure Events
No large multiple case exposure events were found. In Florida in 2004, four cases were exposed to Roundup after their neighbor applied it at the fence line and it subsequently drifted onto the property next door. Three were low in severity and one was moderate in severity.

Exposure Information
The most common single ai glyphosate exposure, responsible for 50% of cases, involved the application of the product. A closer review of the high and moderate severity case narratives (n=63) was conducted. Of the 63 high and moderate cases, 19 were missing case descriptions. Seventeen of the cases with missing narratives are California cases from 1998-2003. Of the remaining 44 high/moderate severity cases with case narratives provided: 16 were exposed while applying the product, eight involved equipment problems while handling the product (leaks, breaks, etc), six various exposure scenarios occurring at non-agricultural workplaces (such as landscape, Walmart), six resulted from ingestion of the product (three of these ingestion cases were high severity), four bystander exposures, two spills while mixing the product, and one child who handled the product. Among the high/moderate severity cases, ocular symptoms were most frequently reported (n=28); followed by dermal (n=25). A summary of case narratives for all moderate and high severity cases are provided in Table 7 below.

Table 7. Case Activity at Time of Exposure in SENSOR-Pesticides (1998-2009)

Code	Activity	Frequency
1	Applying	253
99	Unknown	60
10	Routine outdoor living	55
8	Routine work incl. fieldworkers	52
9	Routine indoor living	36
2	Mixing/loading	15
5	Any combination of 1-4	11
3	Transport or disposal	9
98	Not Applicable	8
4	Repair or maintenance	6
6	Manufacture or formulation	0
7	Emergency response	0
11	Application to self or another	0

Drift Cases

There were 59 glyphosate cases reported that related specifically to drift.

Child Exposures

There were 48 cases reported that involved children under the age of 18 (42 of which were 12 and under) (Tables 8 and 9). In most cases (23), children 6 years old and younger were exposed due to ingestion or tampering with the product.

Table 8. Number of reported glyphosate incidents to children in SENSOR-Pesticides

Age of Child	Incident Count
6 and under	33
7 to 12	10
13 to 17	5
Total	48

Table 9. Age 6 and under case scenarios

Exposure Scenario	Incident Count
Ingestion	12
Child Tampering with product[a]	11
Routine Application	7
Unknown	2
Spill	1
Total	33
[a]Child tampering excludes ingestion, generally involves child spraying self with product resulting in ocular or dermal exposure.	

f. Acute Glyphosate Poisoning Incident Summary

HED previously reviewed glyphosate in 2009 (*Updated Review of Glyphosate Incident Reports*, M. Hawkins and J Cordova, 03/12/2009). From the years 2002 to March 2009, 289 incidents involved products containing the single chemical glyphosate in Main IDS. HED found that "the IDS query resulted in a moderately large number of case reports which warrants searching the following databases for consistency and reproducibility of the poisoning incident data: the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS), the California Pesticide Illness Surveillance Program, and the National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR)." The general findings and conclusions from HED's current review of IDS (for years 2008-2013) agree with those from this previous HED review. HED found a moderately large number of incidents reported to IDS (212 cases reported for the single chemical glyphosate in Main IDS and an additional 6143 incidents involving glyphosate in Aggregate IDS) and analyzed three additional databases and the AAPCC Annual Reports.

HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report, and the other databases and medical literature reviewed. These health effects primarily include dermal, ocular, and respiratory effects. HED did not identify any

aberrant effects outside of those anticipated. While inconvenient for those who suffer adverse health effects, effects are generally mild/minor to moderate and resolve rapidly.

The incident data available from IDS and NPIC suggest that homeowner mixing/loading/ applying (usually due to human errors and container leaks) are responsible for almost half of the reported incidents. SENSOR-Pesticides incident data are consistent with IDS and NPIC, also suggesting that application of glyphosate results in the most reported incidents (50%). However, the SENSOR-Pesticide incidents include both residential and occupational incidents. The incident data available from CA PISP suggests that occupational handling of equipment is responsible for most incidents due to equipment leaks and malfunction.

All of the databases showed the occurrence of childrens' exposures (ranging from 5% to 27% of total cases). Based on the data in SENSOR, IDS, and NPIC, it appears that the childrens' exposures are due to postapplication exposure, accidental ingestion, and tampering with the product. Ocular exposures and symptoms were reported in all of the databases, to both occupational and nonoccupational users, as a result of splash to the face or touching their eyes with the product on their hands. These symptoms primarily included eye irritation, redness, burning and blurred vision.

Trends over time data from IDS (2008 to 2012), PISP (2005 to 2010), SENSOR-Pesticides (1998 to 2009) and AAPCC (2001 to 2012) data were reviewed. Based on IDS and AAPCC, which are primarily non-occupational cases, incidents appear to be decreasing over time. CA PISP data represents both occupational and non-occupational incidents. This data appears to be relatively steady over time. The SENSOR-Pesticide data also represent both occupational and non-occupational cases. For this data, occupational case reports involving glyphosate appeared to be increasing until 2008 and non-occupational case reports appear to be increasing over time. The increase in non-occupational case reports may be reflective of increased SENSOR state capacity to collect non-occupational pesticide surveillance data.

4. CHRONIC DISEASE EPIDEMIOLOGY

In this section, HED discusses the available evidence concerning the chronic health effects of glyphosate exposure in the human population. Environmental epidemiology studies are designed to evaluate whether there is evidence of an increased (or decreased) risk of disease in relation to a specific environmental risk factor such as pesticide exposure. For this report, HED/TEB identified several published, peer reviewed epidemiology studies concerning exposure to glyphosate. A wide variety of cancer and non-cancer health outcomes are included in this analysis.

a. Literature Review Methodology

In preparing this Tier II review of environmental epidemiology data related to glyphosate exposure, HED queried publis6hed, peer-reviewed literature. Appendix 4 describes the methods reviewers utilized to identify, to select, and to evaluate the open literature studies. These methods are in accordance with the OPP Guidance on Open Literature Reviews[5]. Briefly, reviewers developed a comprehensive search string for use in both PubMed and Web of Science, two major biomedical searchable databases available to EPA scientists. Google scholar was also searched for additional unique research articles. Inclusion criteria were a direct epidemiologic measure of glyphosate (as opposed to all herbicides, or all phosphonic acid pesticides), and English language publication. Publication date was not restricted, but most articles were published 1990 to present. HED excluded articles that did not make an epidemiological risk estimate of glyphosate exposure in relation to an adverse health outcome (exposure only, acute toxicity only, experimental toxicology study, ecologic risk study, or other review or commentary), or were not full text articles (e.g., abstract only). There were 90 articles initially identified using the search string; of these, 59 were excluded and 31 included in full text review. Among the 31, only 10 were included in the review. Citation mapping added an additional 40 articles, of which 36 were derived from examination of two recent review articles (Mink, Mandel, Lundin, & Sceurman, 2011; P. J. Mink, J. S. Mandel, B. K. Sceurman, & J. I. Lundin, 2012), and four were identified using citation mapping techniques. An additional 5 articles were identified through the European Food Safety Authority pesticide epidemiology systematic review[6]. Therefore, there are 55 epidemiology studies included in the review of glyphosate evaluating both cancer and non-cancer chronic disease endpoints. A full description of literature review methodology is in Appendix 4 which includes a comprehensive listing of all articles identified and excluded based upon title and abstract review or full text evaluation, and a listing of the final 55 articles included in the review.

b. Summary of Glyphosate Epidemiology Literature

As discussed above, glyphosate is a non-selective herbicide registered for use on a variety of fruit, vegetable, and field crops, as well as for residential uses. Glyphosate can be applied pre- or post-emergence, or during the growing season. Therefore, given the number of use sites and the range of timing of application, the exposure potential is substantial. Available experimental evidence indicates that the acute and chronic toxicity of the pesticide is low by all routes of exposure, and well characterized as a result of submitted guideline studies. Glyphosate has been classified as a "Group E" chemical (evidence of non-carcinogenicity for humans), based upon lack of convincing evidence of carcinogenicity in adequate studies in two animal species (mice and rats). This section presents information pertaining to potential glyphosate toxicity in the human population. Epidemiology study review is important for several reasons: animal data are

[5] http://www.epa.gov/pesticides/science/literature-studies.html
[6] http://www.efsa.europa.eu/en/supporting/pub/497e.htm

not always good surrogates for health effects of chemicals in the human population; the exposure range in animal studies are typically much higher than experienced in "real world" human populations; and, human studies better reflect toxicity of the end-use product, as opposed to the active ingredient as well as exposure to a mixture of compounds. Considering this information, the results of observational studies in the human population are considered herein.

Studies included in this review evaluate both cancer and non-cancer health outcomes. Many of the studies included are from the Agricultural Health Study (AHS); however, there are several analyses from population-based case control studies in other parts of the Midwest, Canada and Europe. In addition, use of glyphosate in the control of illegal crops, *e.g.*, cocaine, is common in some parts of the world; there is one study included which was performed in South America (Columbia), in which this use is prevalent. It should be noted that, with only one exception, all the studies included in this review evaluate glyphosate *in addition to* several (dozen in some instances) other agricultural pesticides in relation to a potential health outcomes; glyphosate was only *a priori* identified as a compound of interest in the cohort study on glyphosate in the AHS in which glyphosate exposure and all cancer risks were compared. While there are several dozen studies included in this review, there may be only a few studies for each chronic health endpoint upon which to assess consistency of findings. Therefore, while the pesticide epidemiology database for glyphosate exposure is large in comparison to other active ingredients, it is still unfortunately limited in making causal inference for specific chronic disease outcomes. A summary of the observational studies of the human health effects of glyphosate is presented in this section.

b.1. Non-Cancer Effects

Epidemiological studies of the potential role of glyphosate, among other compounds, in the etiology of several non-cancer health effects are detailed in this sub-section.

b.1.1. Adverse Birth Outcomes

Several studies evaluated the role of pesticides and increased risk of adverse developmental and reproductive health outcomes. Pesticide exposure in relation to pregnancy complications such as gestational diabetes and increased time to pregnancy (TTP) as well as reproductive conditions like small-for-gestational age (SGA) and low birthweight are included in this section. Study authors also reviewed the potential role of pesticides in adverse birth outcomes such as neural tube defects (NTD), congenital malformations, and spontaneous abortion. A brief summary of these reports is included in this section.

Two studies evaluated time to pregnancy in relation to exposure to pesticides, hypothesizing that pesticide exposure may interfere with fecundability among those exposed. Within the Ontario Farm Family study, Curtis et al. (1999) reported some evidence of increased TTP (40% increase in TTP) among women exposed to glyphosate pre-conception (fecundability rate ratio (FRR)

0.61 (95% CI 0.24, 1.05)). Authors did not observe evidence of increased time to pregnancy given fathers exposure to glyphosate prior to conception (Curtis, Savitz, Weinberg, & Arbuckle, 1999). Authors state they identified no clear pattern of pesticide use in relation to TTP, but use of herbicides in general was more strongly linked to this outcome. The exclusion of sub-fertile and infertile women as well as potential exposure misclassification could have attenuated the effects estimates. However, unmeasured positive confounding and chance could explain positive findings. Authors did not identify any one pesticide as strongly linked to TTP in this study, indicating further research is needed. In a separate investigation using ecologic exposure assessment methods, authors examined use of Roundup (glyphosate end use product) by illicit drug production area. Sanin et al (2009) and colleagues reported some evidence of reduced time to pregnancy among women who reside in areas of Columbia (South America) in which illicit drug eradication programs using glyphosate are of the greatest intensity (FRR 0.15 (0.12, 0.18)) (Sanin, Carrasquilla, Solomon, Cole, & Marshall, 2009). Both studies investigating TTP in relation to pesticide use have uncertainties, making it difficult to draw firm conclusions. The indirect (and ecologic) nature of the pesticide exposure assessment in both evaluations dictate further follow-up before a link with this reproductive health endpoint can be established.

HED also identified studies on pregnancy outcomes such as pre-term delivery and small-for-gestational age in relation to pesticide use. Across these studies, there is little evidence of a role for glyphosate. Savitz et al. (1997) reported a non-statistically significant association between glyphosate use and preterm delivery (OR (95% CI) 1.5 (0.8, 2.7), and no link with SGA (OR (95% CI) 0.80 (0.20, 2.3)) (Savitz, Arbuckle, Kaczor, & Curtis, 1997). However, the authors acknowledge the study requires replication as there is insufficient evidence to suggest a role for any specific pesticide in this study. Garry et al. (2002) evaluated pesticide use and male:female sex ratio in an agricultural area of the U.S., but did not report any glyphosate-specific risk estimate because there was no significant exposure-response relation with this chemical (Garry et al., 2002).

While other pesticide epidemiology studies have reported an association with low birth weight and pesticide exposure (Whyatt et al., 2004), Sathayanarayana et al. (2010) did not observe such a link when considering glyphosate use in the AHS cohort (Sathyanarayana et al., 2010). In the cross-sectional study, authors compared lifetime glyphosate use (as reported by female spouses of male pesticide applicators) and range of pregnancy time period. Other pesticides were marginally linked to low birth weight, but glyphosate was not associated with this outcome. Further Saldena et al. (1999) performed a cross-sectional analysis of pesticide use and gestational diabetes in the AHS cohort. Among 11,273 pregnancies reported among women enrolled in the cohort study, authors did not observe a relation between gestational diabetes and self-reported, ever-use of glyphosate during the first trimester of the most recent pregnancy. While errors in the timing of exposure (misclassification) and residual confounding could have reduced the observed effect estimates, the observation of a link with some pesticides, but not glyphosate, suggest the herbicide may not play a role in GD, based upon the evidence in this study.

There were several studies of birth malformations in relation to pesticide use including glyphosate. Rull et al examined the relation between glyphosate and other pesticides and birth certificate reported incidence of neural tube defects (Rull, Ritz, & Shaw, 2006). Cases (731) were births between 1987-1991 in CA, and pesticide exposure was measured as maternal residential proximity to an agricultural field treated with specific pesticides. Authors reported non-statistically significantly elevated (50%) risk of NTD among glyphosate exposed women, adjusting for education, ethnicity, peri-conception smoking and vitamin use. Results were attenuated upon mutual adjustment for exposure to other pesticides (OR (95% CI) 1.4 (0.8, 2.5)). Authors pooled two population-based case control studies to increase the number of birth defect cases included in the study. However, major findings from this pooled analysis related to other pesticides (methomyl, benomyl), and not glyphosate. The non-significant result could be explained by exposure misclassification (which would not likely be differential since residential address and not self-report was used in exposure assessment), residual confounding by factors negatively related to both pesticide use and NTD, or small number of glyphosate exposed cases. Garcia et al. (1998) initially identified a positive association between congenital malformations and glyphosate (OR (95% CI) 1.23 (0.59, 2.56), but the association attenuated considerably upon mutual adjustment for other risk factors including spontaneous abortion, drug use, smoking, education, occupational exposure to other pesticides, and age (OR (95% CI) 0.94 (0.37, 2.56) (Garcia, Benavides, Fletcher, & Orts, 1998). Arbuckle et al. (2001) reported non-statistically significantly elevated risk of spontaneous abortion among women who were exposed to glyphosate pre-conception (OR (95% CI) 1.7 (1.0, 2.9)) and post-conception (OR (95% CI) 1.4 (0.80, 2.5))(Arbuckle, Lin, & Mery, 2001). There were many strengths of this study including the ability to measure exposure in the pre- and post-conception time periods; however authors of this study urge caution in the interpretation of results because many different statistical tests were performed, and exposure misclassification is possible. Glyphosate exposure was among the key findings of the study (atrazine and carbaryl also associated with spontaneous abortion in this study). Considering the totality of the scientific data concerning adverse birth outcomes, there is little overall evidence of a role for glyphosate at this time.

b.1.2 Respiratory Effects

Within the AHS, authors have made several evaluations of respiratory health effects and pesticide exposure including asthma, chronic bronchitis, rhinitis and wheeze. Each investigation utilized a cross-sectional study design; however, given the study was with the prospective AHS and the use of certain analytic methods, concerns about temporal bias (exposure did not precede onset of respiratory health effect) are somewhat ameliorated. In addition, each study was hypothesis-generating in nature such that all pesticides within the AHS were measured in association with incidence or prevalence of these health effects. Across these studies, there were some observations of positively elevated risks of adverse respiratory health in association with glyphosate use; however, for the most part, other compounds were more strongly associated with respiratory health. Given the hypothesis-generating nature of these studies, many statistical tests

performed and the potential for unmeasured, positive confounding bias that may explain outcomes, more research is needed to clarify whether glyphosate truly plays a role in respiratory health.

Hoppin et al. (2008, 2009) evaluated adult-onset asthma and prevalence of atopy in both men and women enrolled in the AHS. Atopy is the presence of other allergic conditions such as hay fever and eczema. Authors observed elevated odds of asthma among those with and without atopy in both men and also women among those who report use of glyphosate. Results were similar for men and women and did not statistically differ between those with and without atopy (Women: atopic asthma: OR (95% CI) 1.31 (1.02, 1.67); non-atopic asthma: OR (95% CI) 1.13 (0.92, 1.39), p-value 0.40; Men: atopic asthma: OR (95% CI) 1.37 (0.86, 2.17), non-atopic asthma: OR (95% CI) 1.15 (0.87, 1.51)) (Hoppin et al., 2008; Hoppin et al., 2009). Glyphosate was one of two herbicides among 11 different herbicides tested that were statistically significantly association with asthma in this study and chance may therefore play a role; other pesticides were more strongly related to asthma in this study. Rhinitis, or runny nose, was marginally, but significantly, associated with glyphosate use among both private but not commercial applicators (odds at least one rhinitis episode in past year: 1.09 (1.05, 1.13); odds 13+ episodes rhinitis in past year: 1.14 (1.07, 1.21), global p=0.001)) (Slager et al., 2009; Slager et al., 2010). The authors did not observe a relation with chronic bronchitis among either men (OR 0.99 (95% CI (0.82, 1.19)) or farm women (1.07 (95% CI (0.89, 1.29)) (Hoppin et al., 2007; Valcin et al., 2007). There is little evidence of a role for glyphosate in the prevalence of wheeze among either private or commercial pesticide applicators, and risk estimates attenuate considerably upon mutual adjustment for pesticides and chlorimuron-ethyl specifically (Hoppin, Umbach, London, Alavanja, & Sandler, 2002; Hoppin et al., 2006). While these authors note an elevated odds of wheeze among glyphosate users who are not also asthmatics (OR (95% CI) 1.5 (1.1, 2.1)), researchers also note that a healthy worker effect in which applicators with asthma or wheeze avoid chemical exposure, making the effect estimate for non-asthmatics artificially higher than asthmatics (Hoppin et al., 2002). These studies indicate a possible role for pesticides in respiratory health; however glyphosate is not strongly suggested as a risk factor based upon these data.

Overall, while some significantly elevated odds of adverse respiratory health outcomes were observed in relation to glyphosate use, the number of statistical tests, the hypothesis-generating nature of these studies, and the limited ability to co-adjust for other pesticides (particularly in studies of women) render the database insufficient to make a determination of the role of glyphosate in these outcomes.

b.1.3 Other Non-Cancer Effects

HED also identified epidemiology studies of other non-cancer health effects in relation to pesticide use including glyphosate exposure. Endpoints include auto-immune (rheumatoid arthritis) and endocrine (diabetes) effects, dysfunction of the cardiac (myocardial infarction) and

neurological (Parkinson's disease) systems, respiratory health, and retinal degeneration. DeRoos et al. (2005) examined the association between pesticide use including glyphosate and the incidence of rheumatoid arthritis (RA) in a nested case control study in the AHS. Among 135 RA cases and 675 matched controls, authors did not observe a link with RA by self-reported glyphosate use (odds ratio (OR (95% CI) 1.2 (0.8, 1.8)), and there was no difference in risk by study state (IA or NC) (De Roos, Cooper, Alavanja, & Sandler, 2005). Given the cross-sectional nature of the study, disease initiation could have preceded pesticide use (temporal bias) affecting the risk estimate (under-estimate if prevalent cases mixed with new cases). However, authors conclude on the basis of this study that other farm exposures excluding pesticide use may be more strongly related to RA etiology. In another study within the AHS, Kirrane et al. (2005) examined retinal degeneration (RD) among wives of enrolled pesticide applicators in relation to pesticide use. Among 31,173 women enrolled in the study, authors did not observe an association between self-reported, ever-use of glyphosate and RD (OR (95% CI) 1.1 (0.8, 1.5)) (Kirrane et al., 2005).

Kamel et al. (2007) performed an analysis of both incident and prevalent Parkinson's disease (PD) in relation to pesticide use among AHS participants. Among 79,557 private and commercial pesticide applicators, authors identified 83 prevalent and 78 incident cases of PD. PD status was measured as a result of participants self report of a physician diagnosis of the condition (no confirmation). Pesticide use was also measured using the AHS self-report questionnaire from which lifetime exposure days was calculated. Adjusting for age, state and type of applicator (or spouse of applicator), authors did not observe a significant, positive association between glyphosate and either incident (OR (95% CI) 1.1 (0.6, 2.0), or prevalent PD (OR (95% CI) 1.0 (0.6, 1.7)) (Kamel et al., 2007).

Similarly, a study of cardiac effects in relation to pesticide use in the AHS did not identify any links with glyphosate. Because risk factors for heart attack (MI) differ greatly between men and women, authors examined each group in separate studies. Controlling for the age, state, smoking, BMI, and the use of other pesticides (only among men), authors did not observe any association between incident MI or mortality due to MI among either male or female participants in the AHS with glyphosate – relative risks were the null value (1.0) (Dayton et al., 2010; Mills, Blair, Freeman, Sandler, & Hoppin, 2009).

AHS authors also examined diabetes in relation to pesticide use, and did not observe evidence of an association with glyphosate (OR (95% CI) 0.85 (0.74, 0.98) (Montgomery, Kamel, Saldana, Alavanja, & Sandler, 2008). Similarly, AHS study authors found no association between thyroid disease and glyphosate use in a cross-sectional analysis in the AHS; hyper-thyroidism: 0.98 (0.78., 1.2); hypo-throidism: 1.0 (0.91, 1.2); and, "other" thyroid disease: 0.97 (0.81, 1.2) (Goldner et al., 2010).

While these non-cancer health endpoints are wide ranging, in most instances only one study was available for a specific endpoint, therefore making it challenging to assess consistency in the

human population. Across these varied non-cancer, chronic health endpoints, there is little evidence of a role for glyphosate in the etiology of these non-cancer health effects.

b. 2. Cancer Effects

An effect estimate of the relation between glyphosate and other pesticide exposure and several different anatomical cancer sites is included in this literature review. Mainly performed within the AHS cohort, this literature review includes studies of prostate, lung, and colorectal cancer in addition to less common cancers in the human population such as pancreatic and stomach cancer in association with pesticide use. The role of pesticide use and lymphohematopoietic cancers and particularly non Hodgkin lymphoma (NHL) has been studied in several investigations external to the AHS cohort. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available; however, for NHL and other non-solid tumors, several investigations are published. In this section, we present a summary of the studies evaluating the carcinogenic potential of glyphosate and other pesticides in the human population.

b.2.1 Solid Tumor Cancer Studies (non-lymphohematopoietic (LHP) cancers)

Within the AHS study cohort, authors evaluated several anatomical cancer sites in relation to pesticide use. None of these investigations reported a significant statistical association with lifetime use of glyphosate specifically. While these are all initial, hypothesis-generating studies and require further follow-up studies to determine whether the true association with glyphosate is indeed null, the large sample size, extensive exposure data collection and validation, and comprehensive confounding variable adjustment in the AHS supports a conclusion of no association between glyphosate use and cancers studied at this time. In a cohort analysis of all glyphosate users, authors did not observe an association with all cancers combined (OR 1.0 (95% CI (0.90, 1.2)) or specific anatomical cancer sites, with the exception of a non-statistically significantly elevated risk of multiple myeloma based upon a small number of glyphosate exposed cases (De Roos, Blair, et al., 2005). A discussion of studies external to the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in section b.2.2 below.

Several AHS nested case-control analyses also provide information concerning the carcinogenic potential of glyphosate; there is no statistical evidence of an association with glyphosate presented across these investigations. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and breast cancer (OR 0.9 (95% CI (0.1, 1.1)) (Engel et al., 2005), colorectal cancer (OR 1.6 (95% CI (0.9, 2.9)) (W. J. Lee et al., 2007), lung cancer (no results shown due to lack of statistically significant risk estimate) (Alavanja et al., 2004), pancreatic cancer (OR (95% CI) 1.1 (0.6, 1.7)) (Andreotti et al., 2009), and prostate cancer (no results shown due to lack of statistically significant risk estimate) (Alavanja et al., 2003; Koutros et al., 2013), as well as cutaneous melanoma (no results shown due to lack of statistically significant risk estimate) (Dennis, Lynch, Sandler, & Alavanja, 2010). In a

population-based study external to the AHS, Canadian researchers reported non-significantly elevated odds of prostate cancer in relation to glyphosate use (OR 1.36 (95% CI 0.83, 2.25)) (Band et al., 2011). This study enrolled prostate cancer cases between1983-1990, prior to the PSA-era; therefore, the study includes more advanced tumors upon diagnosis, and is not comparable to Alavanja et al. (2003), which reflects cases during the PSA-era in which cases are typically identified at an earlier stage in the natural history of disease. Notably, in a prostate cancer follow-up study within the AHS, Koutros et al. (2013) did not identify an association with advanced prostate cancer (OR (95% CI) 0.93 (0.73, 1.18)) (Koutros et al., 2013). AHS investigators also examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with glyphosate use (maternal exposure to glyphosate: OR (95% CI) 0.61 (0.32, 1.16)); paternal exposure to glyphosate: OR (95% CI) 0.84 (0.35, 2.54)) (Flower et al., 2004).

Brain Tumors (Glioma): Population-Based Case Control Studies: External to the AHS cohort study, HED identified population-based case control studies which evaluated brain cancer in relation to pesticides use. Glioma is the most common type of brain tumor. In a study of ever-use of pesticides, authors identified 251 glioma cases between 1988 and 1993 in Nebraska, and controls (n=498) identified from the same region. Matching for age and vital-status, study authors reported a non-significant elevated odds of glioma (OR 1.5 (95% CI (0.7, 3.1)) in relation to glyphosate use; however the results were significantly different between those who self-reported pesticide use (OR 0.4 (95% CI (0.1, 1.6)), and for those whom a proxy respondent was used (3.1 (95% CI (1.2, 8.2)), indicating recall bias was likely a characteristic of this study (W. Lee et al., 2005). Three other population-based case control studies of glioma risk were part of this literature review; authors investigated the question among men and also among women participating in the Upper Midwest Health Study ((Carreon et al., 2005; Ruder et al., 2004; Yiin et al., 2012). Among glioma cases identified 1995-1997, authors found little evidence of a role of glyphosate in the etiology of this tumor. While herbicide use overall was non-statistically significantly linked to glioma in the study among men (OR 1.51 (95% CI (0.92, 2.48)), use of glyphosate was not linked to glioma among women (OR 0.7 (95% CI (0.4, 1.3). In the study by Carreon et al. (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to the study by Lee et al. (2005) noted above. Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (occupational use: OR 0.98 (95% CI 0.67, 1.43); home and garden use: OR 0.83 (95% CI 0.39, 1.73))(Yiin et al., 2012). Overall, this database presents little statistical evidence that there is a role for glyphosate in glioma risk in the Midwestern U.S.

Adenocarcinoma: Population-Based Case Control Study: In another population based case control study in the Midwest (NE), authors evaluated pesticide use and adenocarcinoma. Researchers did not observe an association between glyphosate exposure and either stomach

cancer (OR (95% CI) 0.8 (0.4, 1.5)) or esophageal cancer (OR (95% CI) 0.7 (0.3, 1.4)) (W. Lee et al., 2004). Exposure assessment was based upon self report pesticide use, with follow-up telephone interview to verify reported information. Cancer cases were identified through the state cancer registry, and confirmed by pathologist. While non-differential misclassification of either pesticide use could have occurred and attenuated or obscured results, it is unlikely there is a strong positive association with glyphosate and adenocarcinoma based the evidence presented in this study.

b.2.2 Non-Solid Tumor Sites (Lymphohematopoietic cancers)

There are several epidemiology studies of the possible link between pesticide use and lymphohematopoietic cancers; the study of NHL is particularly well represented in this small epidemiology database. All studies are case-control in design; there are no prospective cohort evaluations of this potential association. The presence of case control study design across this database limits development of firm causal inference.

Leukemia: In a population-based case control study in Iowa and Minnesota, authors investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR (95% CI) 0.9 (0.5, 1.6)) (Brown et al., 1990). The study population was identified from cancers reported to state registry or authorities in 1981-1984, and pesticide exposure assessment was performed through in-person interview which authors state likely reduced exposure misclassification (incorrect exposure information). The large sample size (578 cases and 1245 controls), exposure assessment methods, and confounding variable control are strengths of the study; however the lack of clear exposure-response information and the potential for recall bias are also present. In another population based case control study, cases were identified in 1987-1992 through the Swedish cancer registry. Authors reported a non statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR (95% CI) 3.1 (0.8, 12.0), controlling for age, gender, and residential location (Nordstrom, Hardell, Magnuson, Hagberg, & Rask-Andersen, 1998). However, these results are based on only 4 and 5 glyphosate exposed cases and controls, respectively, and should be interpreted with caution, as noted by the authors. At this time, the limited available literature concerning glyphosate use and leukemia cannot support a conclusion that glyphosate plays a role in leukemia.

Multiple Myeloma (MM): Using the same study population as noted above in reference to leukemia risk and pesticide use, Brown et al. (1993) studied whether pesticide use is also related to MM. Among men in Iowa (173 cases, 605 controls), authors observed a statistically non-significant elevated association with glyphosate use (OR (95% CI) 1.7 (0.80, 3.6))(Brown, Burmeister, Everett, & Blair, 1993). However, authors caution that while the study may lend support for the role of pesticides in general, the study limitations preclude use of evidence in support of any one compound. In the AHS cohort analysis by de Roos et al. (2005), researchers also reported a non-statistically significantly elevated risk of multiple myeloma among glyphosate users (OR 2.6 (95% CI (0.70, 9.4)), but this results was based upon only 32 MM

cases (20 of whom reported exposure to glyphosate), and authors did not observe evidence of an exposure-response trend by duration or intensity of pesticide use (De Roos, Blair, et al., 2005). Authors suggest there are too few cases of glyphosate exposed MM in the study to make a firm conclusion. In a population-based case control study in Canada, researchers reported non-statistically significantly elevated odds of MM in relation to glyphosate use (OR (95% CI) 1.22 (0.77, 1.93), based upon 32 and 133 glyphosate exposed MM case and controls, respectively (Pahwa et al., 2012). Within the AHS study population, molecular epidemiology researchers studied the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS); MGUS is considered a pre-clinical marker of MM progression. Authors did not observe a link with glyphosate use in the AHS cohort (OR 0.50 (95% CI (0.20, 1.0)) (Landgren et al., 2009). At this time, the epidemiologic database regarding the possible link between pesticide use and MM is too small and inconsistent to determine whether glyphosate plays a role in this cancer.

Lymphoma: The National Cancer Institute (NCI) performed a series of population-based case control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred NHL cases and controls, identified cases through disease registries which in many cases were histopathologically confirmed. Investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time. Early investigations (IA and MN) did not observe a link with ever-use of glyphosate (OR (95% CI) 1.0 (0.5, 2.2)); however authors did not adjust for exposure to other pesticides in this study (Cantor et al., 1992). Pooling data from several Midwestern states to increase study sample size (IA, MN, NE), and using additional pesticide use information to adjust the risk estimate (duration and frequency of use, telephone follow-up interview), Lee et al. (2004) observed a positive, non-significant association with glyphosate among those without asthma (OR (95% CI) 1.4 (0.98, 2.1)), adjusting for age, state and vital status (W. J. Lee, Cantor, Berzofsky, Zahm, & Blair, 2004). In a pooled analysis (n=3,417) of these same three study states, and utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, authors observed a similarly elevated, but non-statistically significant result: OR (95% CI) 1.6 (0.90, 2.8) (De Roos et al., 2003). These three evaluations reflect the same study population, use different levels of information (duration and frequency of exposure) and different analytic techniques (hierarchical regression and stratified analysis (by atopy)). While studies with increasing levels of refinement to method report a stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

Hardell et al. (1999 and 2002) performed two analyses of the possible link between pesticide use and NHL using the Swedish cancer registry and a telephone based exposure questionnaire to determine pesticide use. The initial investigation of 404 NHL cases and 741 control subjects included only 4 and 5 glyphosate exposed cases and controls, respectively. The risk estimate was elevated, but precision was low (OR (95% CI) 2.3 (0.40, 13.0)) (L Hardell & Eriksson, 1999). In

a pooled analysis reflecting the same study time period and prevalence of glyphosate use, Hardell et al. (2002) reported a non-statistically elevated odds of NHL among glyphosate users: OR (95% CI) 1.85 (0.55, 6.20)), however this estimate also lacks precision (L. Hardell, Eriksson, & Nordstrom, 2002). Authors stated glyphosate use was low in the time period of the study 1987-1990. Therefore, authors performed a new study in later time period (1999-2003) in which glyphosate use had increased. In this study, authors observed a similar risk estimate (OR (95% CI) 1.55 (0.77, 2.94)), among 910 NHL cases and 1016 non-NHL controls (Eriksson, Hardell, Carlberg, & Akerman, 2008). Authors conclude that the follow-up study, with a greater number of glyphosate exposed participants lends support to the conclusion glyphosate may play a role in NHL.

Within the Cross- Canada study of pesticides and health, authors estimated the association between glyphosate and NHL as well. These investigations reflect cases identified 1991-1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of cases, and implemented a two-tiered exposure questionnaire, and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the study results. Glyphosate was not among the primary findings of either study. The initial study within this population identified a non-statistically significant 20% increased risk of NHL (OR (95% CI) 1.20 (0.83, 1.74))(McDuffie et al., 2001), which attenuated in a follow-up study which controlled for exposure to other pesticides (OR (95% CI) 0.92 (0.54, 1.55)) (Hohenadel et al., 2011). Within this series of studies, authors also evaluated Hodgkin lymphoma (HL), and similarly observed little statistical evidence of an association, using similar study design and methods (OR (95% CI) 0.99 (0.62, 1.18)) (Karunanayake et al., 2012). In a separate study using a hospital-based case control study design (France (2000-04)), authors identified 491 NHL cases and 456 non-cases, and performed telephone-based questionnaire to assess pesticide and other confounding variables. Investigators did not observe an association between NHL and glyphosate use (OR (95% CI) 1.0 (0.50, 2.2)) (Orsi et al., 2009).

c. Glyphosate Summary

HED identified 55 environmental epidemiology studies regarding potential cancer and non-cancer, chronic health effects in association with pesticide use including glyphosate. As noted above, few of these studies reflected an *a priori* research interest in the potential role of glyphosate and chronic disease outcomes. Most studies were hypothesis-generating in nature, and study authors evaluated use of glyphosate in addition to several other pesticides. Therefore, the role of chance given the many different statistical tests performed and the lack of a pre-specified hypothesis limit epidemiologic inference. Given this and other limitations of these studies, we cannot conclude glyphosate plays a role in any of the health outcomes studied across this epidemiologic database. EPA will continue to follow the literature concerning the potential role of the chemical in respiratory health (asthma in particular), as well as adverse pregnancy and birth outcomes such as increased time to pregnancy. Across the several population-based case-control studies on NHL and pesticide use, some investigators observed non-statistically

significantly increased risk in relation to glyphosate use, while others reported no observation of a statistical association with glyphosate use. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could explain these inconsistencies in the data. A prospective study devoid of the limitations of exposure recall inherent to case control studies will greatly aid causal inference. EPA will await with interest any new study using prospective exposure assessment methods to investigate the role of glyphosate and NHL and other lymphohematopoietic tumors.

5. CONCLUSIONS

The relatively high number of reported glyphosate incidents across the reviewed databases is likely a result of glyphosate being among the most widely used pesticides by volume. It should be noted that, most of the incidents reported are minor in severity meaning the symptoms were minimally traumatic and resolved rapidly.

HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report, and the other databases and medical literature reviewed. These health effects primarily include dermal, ocular, and respiratory effects. HED did not identify any aberrant effects outside of those anticipated. While inconvenient for those who suffer adverse health effects, effects are generally mild/minor to moderate and resolve rapidly.

The incident data available from IDS and NPIC suggest that homeowner mixing/loading/ applying (usually due to human errors and container leaks) are responsible for almost half of the reported incidents. SENSOR-Pesticides incident data are consistent with IDS and NPIC, also suggesting that application of glyphosate results in the most reported incidents (50%). However, the SENSOR-Pesticide incidents include both residential and occupational incidents. The incident data available from CA PISP suggests that occupational handling of equipment is responsible for most incidents due to equipment leaks and malfunction.

All of the databases showed occurrence of children's' exposures (ranging from 5% to 27% of the total). Based on the data in SENSOR, IDS, and NPIC, it appears that the childrens' exposures are due to postapplication exposure, accidental ingestion, and tampering with the product. Ocular exposure and symptoms were reported in all of the databases, to both occupational and nonoccupational users, as a result of splash to the face or touching their eyes with the product on their hands. These symptoms primarily included eye irritation, redness, burning and blurred vision.

Trends over time data from IDS (2008 to 2012), PISP (2005 to 2010), SENSOR-Pesticides (1998 to 2009) and AAPCC (2001 to 2012) data were reviewed. Based on IDS and AAPCC, which are primarily non-occupational cases, incidents appear to be decreasing over time. CA PISP data represents both occupational and non-occupational incidents. This data appears to be relatively

steady over time. The SENSOR-Pesticide data also represent both occupational and non-occupational cases. For this data, occupational case reports involving glyphosate appeared to be increasing until 2008 and non-occupational case reports appear to be increasing over time. The increase in non-occupational case reports may be reflective of increased SENSOR state capacity to collect non-occupational pesticide surveillance data.

Although animal studies showed glyphosate to have limited toxicity, medical case reports suggest that glyphosate end use products (formulated with different glyphosate salts and various concentrations of surfactants and adjuvants), may be more toxic than the active ingredient alone. Since human poisoning reviewed were not with the active ingredient (glyphosate) alone but with various mixtures, it is not easy to identify the exact cause. Nevertheless, the medical literature reviewed indicates that most of the accidental ingestions of glyphosate formulations resulted in mild symptoms such as irritation of oral and upper gastrointestinal mucosa and were self limited. However, intentional ingestions caused moderate to severe symptoms in multiple organs.

While HED identified several dozen glyphosate environmental epidemiology studies, few of these studies reflected an *a priori* research interest in the potential role of glyphosate and chronic disease outcomes, and most studies were hypothesis-generating in nature. Given this and other limitations of these studies, we cannot conclude glyphosate plays a role in any of the health outcomes studied across this epidemiologic database. EPA will continue to follow the literature concerning the potential role of the chemical in certain cancer and non-cancer outcomes. There were several (case control) studies evaluating the role of pesticide exposure including glyphosate and lymphohematopoietic cancers like NHL however limitations of study design and exposure assessment methods restrict the ability of these studies to inform causal inference. A prospective study devoid of the limitations of exposure recall inherent to case control studies could greatly clarify the current database. EPA will await with interest any new study using prospective exposure assessment methods to investigate the role of glyphosate and NHL and other lymphohematopoietic tumors.

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Appendix 1

Table A: Glyphosate Formulations Identified by the U.S. Forest Service (Diamond, 2011)

Formulation Name	Supplier	EPA Reg. No.	Form	Salt	%a.i.	Surfactant	Other
Accord	Monsanto	524-326	L	IPA	41.5%		Aq
Accord Concentrate	DowAgro Sciences	62719-324	L	IPA	53.8%		
Accord SP	DowAgro Sciences	62719-322	L	IPA	41%	X	No longer available
Accord XRT	DowAgro Sciences	62719-517	L	IPA	53.6%	X-[10]	
Accord XRT II	DowAgro Sciences	62719-556	L	DMA	50.2%	Inferred	
Aqua Star	Albaugh, Inc.	42750-59	L	IPA	53.8%	?[7]	
AquaMaster (a.k.a. Export and Rodeo)	Monsanto	524-343	L	IPA	53.8%		Aq
AquaNeat	Riverdale	228-365	L	IPA	53.8%		Aq
Buccaneer	Tenkoz Inc	55467-10	L	IPA	41.0%	X	
Buccaneer Plus	Tenkoz Inc	55467-9	L	IPA	41.0%	X	
Cornerstone	Winfield Solutions Agrisolutions	1381-191 71368-20-	L	IPA	41.0%	X	
Cornerstone Plus	Winfield Solutions	1381-192	L	IPA	41.0%	?	
Credit Extra	Nufarm	71368-65	L	Am K	17.86% 16.26%	X POEA?	
Credit Systemic Extra	Nufarm	71368-20	L	IPA	41.0%	X POEA?	
Diamondback	EZ-Ject	83220-1	Sh	IPA	83.5%		Injection
DuraMax	DowAgro Sciences	62719-556	L	DMA	50.2%	Inferred	
Durango (GF-1279)	DowAgro Sciences	62719-517	L	IPA	53.6%	X-[10]	
Durango DMA (GF-1280)	DowAgro Sciences	62719-556	L	DMA	50.2%	Inferred	
Eliminator [4,6]	Gro Tec, Inc	71995-27	L	IPA	41.0%	X	
Foresters' Non Selective	Riverdale	228-381	L	IPA	53.8%	None[8]	
Glyphogan	Makhteshim Agan	66222-105	L	IPA	41.0%	Inferred	
Glyphomax 41 Plus [4]	DowAgro Sciences	62719-322	L	IPA	41.0%	Inferred	
Glyphomax XRT	DowAgro Sciences	62719-517	L	IPA	53.6%	X-[10]	
Gly Star Plus	Albaugh Inc	42750-61	L	IPA	41.0%	X	
Glyphosate VMF	DuPont	352-609	L	IPA	53.8%		Cancelled ?
Glyphosate 41 Plus	CropSmart	42750-61-	L	IPA	41.0%	?	
GlyphoMate 41 or Pronto	PBI/Gordon Corporation	2217-847	L	IPA	41.0%	X	
Glyfos Aquatic	Cheminova A/S	4787-34	L	IPA	53.8%		Aq
Glyfos X-TRA	Cheminova A/S	4787-23	L	IPA	41.0%	X 15%[6]	
Glypro	DowAgro Sciences	62719-324	L	IPA	53.8%		
Gly-4 Plus	Universal Crop Protection Alliance	72693-1	L	IPA	41.0%	X	
Helosate Plus	Helm Agro US,	74530-4	L	IPA	41.0%	Inferred	

Formulation Name	Supplier	EPA Reg. No.	Form	Salt	%a.i.	Surfactant	Other
Hi-yield Killzall	Voluntary Purchasing	67760-49-7401		IPA	53.8%		Aq
Honcho (RoundupOriginal)	Monsanto	524-445	L	IPA	41.0%	X	
Honcho Plus	Monsanto	524-454	L	IPA	41.0%	X	
Imitator Plus	Drexel Chemical	19713-526	L	IPA	41.0%	?	
KGro Grass and Weed	Swiss Farms Pdts	71995-27-	L	IPA	1.92%		
Mirage	Loveland Products	34704-866	L	IPA	41.0%	Inferred	
Ranger Pro	Monsanto	524-517	L	IPA	41.0%	X	
RapidFire	DowAgro Sciences	62719-556	L	DMA	50.2%	Inferred	
Rattler	Monsanto	524-445-ZE-	L	IPA	41.0%		
Razor	Nufarm	228-366 [1]	L	IPA	41.0%	X 8%[8]	
Razor Pro	Nufarm	228-366 [1]	L	IPA	41.0%	X 14%[8]	
Rodeo	DowAgro Sciences	62719-324	L	IPA	53.8%		
Roundup Original Max	Monsanto	524-539 [3]	L	K	48.7%	X	
Roundup Pro	Monsanto	524-475 [2]	L	IPA	41.0%	X 14.5%	
Roundup Pro Concen.	Monsanto	524-539 [3]	L	IPA	50.2%	X 13%	
	Monsanto	524-505	G	Am	71.4%	X	
Roundup ProMax	Monsanto	524-579	L	K	48.7%	X	
Roundup UltraMax	Monsanto	524-512	L	IPA	50.2%	X	
Roundup UltraDry	Monsanto	524-504	G	Am	71.4%	X 25%	
Roundup WeatherMax	Monsanto	524-537	L	K	48.8%	X	
RT 3	Monsanto	524-544	L	K	48.8%	X	

[1] Razor and Razor Pro appear to have the same EPA Registration number but the formulations are different.

[2] Based on the EPA master product label, this registration number applies to the following brand names: Roundup Ultra Herbicide; Roundup Ultra RT Herbicide; Roundup Pro Herbicide; Roundup Original II CA; MON 77360 Herbicide; Roundup W Herbicide; Gly 41 Herbicide.

[3] Based on the Product Labels and MSDSs, Roundup Original Max and Roundup Pro Concentrate have the same EPA registration number but contains different salts of glyphosate.

[4] Need specimen label. The EPA labels are not clear (are ambiguous) in terms of the formulation(s) covered.

[5] MSDS cannot be located, including searches of http://www.msdsonline.com and http://www.cdms.net.

[6] From Laimanovich et al. 2003 but not specifically identified as Glyphos Plus.

[7] Bringolf et al. (2007) state that Aqua Star does not contain the MON 0808 POEA surfactant. It is not clear whether or not this formulation contains a less toxic surfactant.

[8] Information confirmed by Nufarm (Ehresman 2010a).

[9] Dow (Fonseca 2010a) has indicated that Accord SP (EPA Reg. No. 62719-322) is not longer commercialized.

[10] Based on information provided by Dow AgroSciences (Fonseca 2010a)

Key:

Form: L=Liquid; G=Granular; Sh=Shells.

Salt: Am=Ammonium salt: DMA=Dimethylamine salt; IPA=Isopropylamine salt; K=Potassium salt;

Other: Aq=Aquatic application; Inj=Injection.

Formulations containing herbicides other than glyphosate as the a.e. are not included.

Table B: Summary of References for the Medical Literature Search		
Study	**Author**	**Summary**
1. Rosen's Emergency Medicine: Concepts and Clinical Practice. 6th ed.	Aaron CK. (2006)	Glyphosate inhibits the enzyme 5-enolpyruvyl-shikimic-3-phosphate-synthase in plants; however, mammals do not have this enzyme.
2. Annual Report	American Association of Poison Control Centers (2011)	According to the American Association of Poison Control data in 2011, glyphosate ranked first with 3,570 exposures among reported human exposures to herbicides (total of 8377); 90% were unintentional.
3. Skin Toxicity from Glyphosate-Surfactant Formulation	Amerio P., Motta A.et al. (2004)	A 78 year old woman presented with extensive chemical burns on her back, knees and legs caused by accidental contact with a glyphosate-surfactant formulation. Sheets of necrotic epidermis had sloughed, leaving extensive erosions. Bullae were present on the dorsum of the feet.
4. Glyphosate poisoning.	Bradberry SM. (2004)	The mechanisms of toxicity of glyphosate formulations are complicated. Not only is glyphosate used as five different salts but commercial formulations of it contain surfactants, which vary in nature and concentration. Ingestion of >85 mL of the concentrated formulation is likely to cause significant toxicity in adults.
5. Extreme hyperkalemia in a patient with a new glyphosate potassium herbicide poisoning: report of a case.	Bando H., Murao Y, (2010)	Ingestion of Roundup Maxload which contains high concentration of glyphosate potassium can cause extreme hyperkalemia with cardiac toxicity and metabolic acidosis.
6. Clinical impact of upper gastrointestinal tract injuries in glyphosate-surfactant oral intoxication.	Chang C.Y., (1999)	Authors studied lesions in gastrointestinal tract of 50 patients with glyphosate-surfactant oral ingestion as a suicide attempt. They found that esophageal injury was seen in 68% of the patients; gastric injury in 72%, and duodenal injury in 16%.
7. Refractory cardiopulmonary failure after glyphosate surfactant intoxication: a case report.	Chang CB, Chang CC (2009)	Patient ingested about 400 mL of concentrated glyphosate developed shock, respiratory failure, hyperkalemia, and acidosis. In spite of comprehensive supportive treatment, patient died 3 days after admission.
8.The epidemiology of glyphosate-surfactant herbicide poisoning in Taiwan, 1986-2007: a poison center study.	Chen YJ, Wu ML, Deng JF, Yang CC (2009)	A retrospective analysis of all GlySH exposures reported to the Taiwan National Poison Control Center between 1986 and 2007. Irritation of the oral mucous membrane and gastrointestinal tract was the most frequently reported effect. Other effects recorded were pulmonary dysfunction, oliguria, metabolic acidosis, hypotension, leukocytosis and fever. Cardiovascular collapse and respiratory failure were two major cause of fatality (Y. J. Chen, Wu, Deng, & Yang, 2009).
9. Glyphosate Human Health and Ecological Risk Assessment (USDA)	Durkin PR (2011)	Authors mentioned that there were various concentrations of POEA surfactant, glyphosate salts and other ingredients in different glyphosate products and the resulting adverse health effects may be different.
10. Handbook of Pesticide Toxicology, 2nd edition (Inhibitors of Aromatic Acid Biosynthesis).	Farmer D., (2001)	Glyphosate contains a carbon and phosphorous moiety but it is not a cholinesterase inhibitor and does not affect the nervous system in the same way as organophosphate insecticides
11. Pesticide-Associated Pemphigus Vulgaris	Fisher KR., et al., (2008)	Described a patient who developed pemphigus vulgaris (PV) on his body and extremities, after an occupational exposure to fumes of burning empty glyphosate drums. PV is an autoimmune skin lesions characterized by bullae that rupture quickly and progress to crusted erosions.
12. **Determination of the herbicide glyphosate and its metabolite in**	Hori, Y.	Authors described the method for determining glyphosate and its metabolites by GC-MS.

biological specimens by gas chromatography-mass spectrometry. A case of poisoning by roundup herbicide		
13. Herbicide roundup intoxication: successful treatment with continuous renal replacement therapy.	Hour BT., Belen C., Zar T., Lien YH., (2012)	Roundup toxicity is mainly due to surfactant, which interferes with the mitochondrial wall, destroying the proton gradient required for energy production. Patient develops cardiogenic shock, lactic acidosis and multiorgan failure. Early administration of hemodialysis would be the treatment of choice (Hour, Belen, Zar, & Lien, 2012).
14. Erythema multiforme like eruption due to an irritant contact dermatitis	**Heras-Mendaza F., et al. (2008)**	A 37-year –old female was exposed to glyphosate herbicide (Touchdown Premium) when the backpack containing the herbicide broke and wet her clothing. She suffered from the irritant contact dermatitis, followed by erythemato-purpuric plaques developed on the upper extremities, on the abdomen, axilla and groin.
15. Glyphosate-surfactant herbicide products containing glyphosate potassium salt can cause fatal hyperkalemia if ingested in massive amounts.	Kamijo Y, Mekari M, (2012)	A 69-year old female ingested about 500 mL of Roundup Maxload contains 48% glyphosate potassium developed severe hyperkalemia and refractory ventricular tachycardia. It was considered that hyperkalemia was caused by Roundup Maxload which contains potassium 2.6 mEq/mL. Endoscopy showed pharyngeal edema, esophageal and gastric erosions.
16. Early continuous dialysis in acute glyphosate-surfactant poisoning.	Knežević V. (2012)	A 36-year old male took about 300 ml of glyphosate-surfactant, six hours later he developed hypotension, oliguria and renal failure. Hemodialysis brought the complete recovery of renal function on the 5th day (Knezevic et al., 2012).
17. Clinical presentations and prognostic factors of a glyphosate-surfactant herbicide intoxication	Lee H.L., Chen K.W., Chi C.H., Huang J.J., Tsai L.M., (2000)	Retrospective review of 131 cases in Taiwan University hospital. The most common symptoms included sore throat (79.5%), and nausea with or without vomiting (73.8%). The most common laboratory findings were leucocytosis (68.0%), low serum bicarbonate (48.1%), and acidosis (35.8%).
18. The early prognostic factors of glyphosate-surfactant intoxication.	Lee C-H, Shih CP, Hsu KH, Hung DZ, Lin CC. (2008)	GlySH poisoning is multiorgan toxicity. Metabolic acidosis, hyperkalemia, respiratory distress needing intubation, tachycardia, and elevated serum creatinine level are useful prognostic factors for predicting GlySH mortality.
19. Severe adverse effects related to dermal exposure to a glyphosate-surfactant herbicide	Mariager TP., Madsen PV ., (2013)	A 43-year old man diluted the glyphosate-surfactant herbicide with water and shook the bottle; the contents accidentally sprayed on him. He did not wash the exposed areas. The next day he developed local swelling, bullae and exuding wounds on right hand, arm, upper arm and axilla regions. Soon it changed into second degree skin necrosis with detachment of the epidermis. In addition he had touched his face with contaminated hands resulting in a peri-orbital edema. Nerve conduction study (NCS) showed reduced nerve conduction in distal axons on the medial, ulnar and radial nerves. Imaging revealed edema of the soft tissue and osteopenia of carpal bones.
20. Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity.	Mesnage R, Bernay B, Séralini GE. (2012)	All formulations are more toxic than glyphosate. Polyethoxylated tallowamine POE-15 appears to be the most toxic principle against human cells (cell membrane disruption and necrosis). Since pesticides are always used with adjuvants that could change their toxicity, it is necessary to assess the toxicity of whole formulations in addition to the active ingredient (Mesnage, Bernay, & Seralini, 2013).
21. Glyphosate–surfactant herbicide-induced reversible encephalopathy.	Malhotra R.C., Ghia DK.(2010)	A 71-year-old male who attempted suicide with GlySH developed a prolonged (clinically unresponsive for more than 7 days, demonstrated with electroencephalogram) but reversible encephalopathy suggestive of the acute central nervous system (CNS) toxicity of the product.

22. Glyphosate based pesticides affect cell cycle regulation.	Marc J. et al., (2004)	Glyphosate based pesticide products disrupt cell-cycle control mechanisms, which may be relevant for cancer as well as noncancer health outcomes.
23. Comparative effects of the Roundup and glyphosate on mitochondrial oxidative phosphorylation.	Peixoto F (2005).	The potential toxicity of the herbicide Roundup and its fundamental substance (glyphosate) was tested in isolated rat liver mitochondria. Roundup interferes electron transfer (by partially inhibiting mitochondrial complexes II and III) and depresses ATPase activity, while glyphosate used in the same concentrations does not induce any significant effect.
24. Acute glyphosate-surfactant poisoning with neurological sequels and fatal outcome	Potrebić O, Jović-Stosić J, (2009)	A 56 year old woman ingested about 500 mL of herbicide containing glyphosate isopropylamine salt developed hypotension, hyperkalemia, respiratory and renal failure, coma and had a lethal outcome. MRI revealed bilateral extensive white matter lesions of the brain stem and Pons.
25. Herbicide (Roundup) pneumonitis.	Pushnoy LA, Avnon LS, Care RS (1998).	A 42-year old worker had inhaled Roundup while cleaning the spraying device in a confined space. He developed shortness of breath, irritative cough, dizziness and hemoptysis. Otolaryngology evaluation showed signs of burns in the mucosal membranes of the pharynx and larynx. Chest X-ray showed acute massive pneumonitis.
26. Dysphonia following glyphosate exposition	Ptok M (2009)	A 26-year-old teacher who used glyphosate formulation correctly but suffered from severe dysphonia after few hours. Laryngoscopy revealed decreased vocal fold mobility suggesting innervation impairment. The symptoms resolved spontaneously 6 weeks later and vocal fold mobility returned to normal.
27. A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning	Roberts DM. et al (2010)	601 cases of intentional ingestion between 2002- 2007 in two hospitals in Sri Lank were followed. 86% of patients had mild symptoms and signs such as nausea, vomiting, diarrhea, abdominal pain, transient hypotension, and tachypnea (respiratory rate >25/minute). 5.5% of patients were in moderate to severe condition with depressed level of consciousness, had respiratory failure and severe hypotension (mean arterial blood pressure <70 mmHg). 3.2% of cases were fatal (median time to death was 20 hours). Glyphosate plasma concentration >734 μg/mL was the best predictor of fatality. Glyphosate product was rapidly absorbed from the GI tract, followed first-order elimination with a half-life ranged from (2.7-3.6) hours.
28. Pathological and toxicological findings in glyphosate-surfactant herbicide fatality: a case report.	Sribanditmongkol P, Jutavijittum P, (2012)	A 37-year-old woman intentionally ingested approximately 500 mL of concentrated Roundup formulation (41% glyphosate as the isopropylamine salt and 15% polyoxyethylene amine). The postmortem examination revealed hemorrhagic areas in the gastric mucosa of anterior fundus and the small intestines had marked dilatation and thin walls. The glyphosate levels of serum and gastric content were 3.05 and 59.72 mg/mL, respectively.
29. Aseptic meningitis in association with glyphosate-surfactant herbicide poisoning.	Sato C, et al (2011)	Patient demonstrated Kernig's sign and significant neck stiffness with rigidity of the extremities as well as consciousness disturbance and fever (38.4°C). Investigations of cerebrospinal fluid (CSF) revealed the presence of glyphosate (122.5 μg/mL), significant elevation of IL-6 (394 μg/mL), and pleocytosis (32 cells/μL) with monocyte dominance. All bacteriological and virological tests were negative.
30. Glyphosate herbicide formulation: A potentially lethal ingestion.	Stella J, Ryan M. (2004)	Although glyphosate is generally regarded as minimally toxic, severe poisoning with glyphosate formulation may be refractory even to the most intensive supportive care. The triad of pulmonary edema, metabolic acidosis and hyperkalemia indicates poor outcome. Polyethoxylated tallowamine (POEA) toxicity can cause gastric pain, pulmonary edema, impaired consciousness and hemolysis. Glyphosate alone can

		also cause gastrointestinal erosions, renal toxicity, metabolic acidosis and central nervous system effects.
31. Roundup intoxication and a rationale for treatment.	Sampogna R.V., Cunard R. (2007)	Patient developed acute renal failure with oliguria after ingestion of Roundup. His condition improved rapidly and renal function returned to normal with hemodialysis treatment (Sampogna & Cunard, 2007).
32. Rapid lethal intoxication caused by the herbicide glyphosate-trimesium (Touchdown).	Sorensen FW, Gregersen M., (1999)	A 6-year-old boy who accidentally ingested a mouthful of glyphosate-trimesium died within few hours. The same happened to a 34-year-old woman who intentionally ingested approximately 150 ml of glyphosate-trimesium. The speed of which death occurs is much more rapid than lethal intoxications with glyphosate (isopropylamine salt), also known as 'Roundup'.
33. Acute Poisoning with a Glyphosate-Surfactant Herbicide ('Roundup'): A Review of 93 Cases	Talbot (1991)	The average amount of the 41% solution of glyphosate surfactant herbicide ingested by lethal cases was 184 ± 70 ml (range 85-200 ml). There were erosion of gastrointestinal tract, pulmonary, renal and central nervous system dysfunction. Deaths followed refractory hypotension or pulmonary edema.
34. Glyphosate Induced Severe Tubulointerstitial Nephritis Requiring Hemodialysis.	Yoo SH, Kim BS, Lee HY., (2010)	Reported the first case of glyphosate induced severe tubulointerstitial nephritis (not secondary to cardiovascular collapse) requiring hemodialysis. Kidney biopsy revealed drug-induced nephrotoxic injury. Patient had ingested about 90 mL of the product.
35. Parkinsonism after chronic occupational exposure to glyphosate	Wang G., Fan X-N., (2011)	A 44 year old woman who worked exclusively at the glyphosate production division for 3 years, 50 hours each week, wearing only basic PPE (gloves or face mask) was diagnosed with Parkinsonism syndrome. She had weakness, dizziness, and blurred vision. She also had a resting tremor, global akinesia and rigidity in all four limbs. MRI revealed bilateral hypotense lesions in the globus pallidus, the substantia nigra and in the cerebral peduncle.
36. Determination of glyphosate in heart blood of corpse by ion chromatography.	Wang Y., et al., (2012)	Ion chromatography is a simple, sensitive and accurate method to prove that the patient had a glyphosate poisoning.
37. Rhabdomyolysis from an intramuscular injection of glyphosate-surfactant herbicide.	Weng SF, Hung DZ, Hu SY, Tsan YT, Wang LM (2008)	Authors described the Rhabdomyolysis (destruction of muscle cells) in the upper limb due to intramuscular injection with the glyphosate product in a suicide attempt (Weng, Hung, Hu, Tsan, & Wang, 2008).
38. Determination of glyphosate and AMPA in blood and urine from humans: About 13 cases of acute intoxication.	Zouaoui K, Dulaurent S, Gaulier JM, Moesch C, Lachâtre G. (2013)	In mild to moderate intoxications blood glyphosate concentrations had a mean value of 61mg/L (range 0.6-150mg/L), in severe intoxication cases, the blood glyphosate concentrations were around 838mg/L and in fatal cases 4146mg/L (range 690-7480mg/L).

Appendix 2

Human Incidents	Chemical: Glyphosate	PC Code: 103601, 103603, 103604, 103605, 103607, 103608, 103613, and 417300

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
019417 - 00001	1/1/2008	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	A 74 year old male ingested 1/2 gallon of Roundup Concentrate. He experienced vomiting, diarrhea and high blood pressure
019542 - 00001	1/1/2008	CA	071995-00032	ROUNDUP WEED AND GRASS KILLER READY TO USE PLUS	103601	MODERATE	The caller states that she is a medical doctor calling on behalf of her friend who has been suffering from Roundup poisoning for years. The caller states that her friend self diagnosed the Roundup poisoning. The woman is being treated for chronic fatigue syndrome and was prescribed to give herself heparin weekly for the condition. She was giving herself heparin that was manufactured in China and it had a hyper sulfur content. She is the only person of her MD's patients who reacted adversely to the heparin getting skin pain and flushing. The patient also has history of asthma but is not compliant with any therapies for the asthma. The caller is not treating the woman. PCC confirmed the exposure was when the gardener sprayed the product outside her home.
019726 - 00001	3/1/2008	HI	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Man was working with Roundup Herbicide unknown formulation about four weeks ago. He does not have the container to confirm the product ingredients. He stated while mixing the product he got some on his hands. He did not wash with soap and water until a few hours passed. The next day his hands were a reddish brown then light redness and the skin sloughed off. His hands are now discolored and sensitive. He has not seen a doctor. At the end of the conversation, he mentioned he is a chemist and works with chemicals. He usually does not get anything on his hands as he wears protective gloves.
019727 - 00001	6/3/2008	CA	000524-00475	ROUNDUP PRO	103601	MODERATE	A worker got overspray from Roundup PRO in his eyes about 1 0 days ago. He rinsed his eyes on the sight and has been to the eye doctor. He has been prescribed eye drops for the last 10 days but his eyes are red and still irritated. He is worried about

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							long term damage to his eyes or if there is something else he should be doing. Follow up indicated that one of the problems with eye drops is an allergic reaction to the drops. There are also some nasal symptoms, so an allergy to the eye drops is likely. He went to MD who advised him to stop using the drops.
019740 - 00001	5/7/2008	SILER CITY, NC	004787-00023	GLYFOS X-TRA	103601	MODERATE	A 36 year old male reports product was sprayed in his face and nose due to the fact that he claimed his sprayer was not attached correctly. There was no skin irritation; however, he reportedly started getting a cough, nasal discharge and a fever the next day. After examination by a doctor, caller reports symptoms were due to pneumonia. He was given antibiotics.
019741 - 00001	6/24/2008	NC	004787-00023	GLYFOS X-TRA	103601	MODERATE	A 51 year old male had product blown back on him by wind as he applied it. The product got primarily his face, head, arms and legs. Approximately 12 hours later, this man reportedly had a blotchy rash all over his head, arms, back, legs and chest with welts on his back and side. After an examination by a doctor, caller states husband was diagnosed with poison oak.
019746 - 00001	5/7/2008	HEATH, OH	004787-00023	ACE READY-TO-USE WEED & GRASS KILLER 2	103601	MODERATE	A 73 year old female reportedly got some product on her shoes. After wearing these same shoes the following Monday, caller noticed her feet were red and burning. Following soaking her feet in apple cider vinegar, caller claimed the skin on her feet was peeling off. Medical treatment was sought and caller was prescribed topical medication. Approximately three and 1/2 weeks later, caller reported having medical evaluation done and symptoms were resolving.
019772 - 00004	5/19/2008	READING, PA	062719-00322	GLYPRO PLUS HERBICIDE	103601	MODERATE	A 28 year old female states that on Tuesday she was spraying the dilute product and when she finished she removed the top of the sprayer and was hit "across her eyes" with the mist of the product. She didn't feel anything go into her eyes nor did she feel any discomfort at the time. She

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							states that last night while doing some trimming with her 'weed whacker' she got some grass in her eye. She couldn't get it out and so she went to the MD who rinsed her eye and gave her antibiotic eye drops. She is now wondering if the product could have also been involved with the irritation. She was asymptomatic before getting the grass in her eye.
019803 - 00001	6/11/2008	HI	034704-00890	KLEENUP PRO HERBICIDE	103601	MODERATE	An adult female was using product at her workplace. The product was mixed 2.5oz per gallon of water. The hose kept coming off and the diluted product saturated her gloves and pants. It was about 1 hour before she could rinse her skin. The next day she experienced decreased urine output, headache and nausea. Her headache and nausea resolved in 24 hrs. She went to MD to address her decreased urination and was diagnosed with a UTI. She was placed on antibiotic and her symptoms resolved.
019862 - 00002	5/7/2008	PA	071995-00032	ROUNDUP WEED AND GRASS KILLER READY TO USE	103601	MODERATE	Caller states that she was using Roundup Ready to Use yesterday morning for about 30 minutes and there was no noted exposure to the product except that she felt like she was breathing it in. She began to have symptoms of vomiting, bloody diarrhea.
019862 - 00007	5/27/2008	CA	071995-00023	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	103601	MODERATE	Caller states his spouse used a Roundup Ready to Use formulation one year ago. Some of the Roundup got onto her hands during the spraying. She did not wash her hands for several hours, until after the project was completed. No skin irritation or rash reported at the time of the exposure or near post-exposure. Husband calling the MRPC to see if the product is absorbed through the skin. His spouse has been diagnosed with squamous cell cancer. He wonders if this could be related to the use of Roundup with dermal exposure.
019862 - 00008	5/27/2008	IL	071995-00023	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	103601	MODERATE	Grandmother calling about her 5 year old granddaughter who, along with some friends, used a gallon of Roundup Weed and Grass Killer Ready to Use. They used the entire bottle on the weeds. There may have been some dermal exposure, but the children were bathed that day. There were no

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							complaints of a sore throat or nasal symptoms on the day of the exposure. The 5 year old female developed a cough and fever was diagnosed with pneumonia four days later. She is going to see a pulmonologist in one month. The caller would like to know if the child is poisoned. Caller states to her knowledge, none of the other children have been sick.
019862 - 00009	5/10/2008	IA	000524-00343	AQUAMASTER	103601	MODERATE	Mother calling about 24 year old son that was pulling out cattails by hand about 5-7days post herbicide treatment with Aquamaster mixed per direction with a nonionic surfactant. Unknown if he was wearing gloves at the time, but he did have on waders. Exposure was greater than six months ago. Since that time he has complained of sneezing, coughing, nasal drainage, gastrointestinal upset and headache. Man has been evaluated by PMD to rule out gastric reflux. He was also evaluated by ENT physician. Mother is calling today as she and son have noted a similar odor of product on son's breath recently. Man denies any oral exposure and questions inhalation of substance during time of dermal exposure. No recent contact with product.
019862 - 00010	5/15/2008	IN	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	Caller states that several years ago (2-3 years), she used a Roundup product or another herbicide to kill some poison ivy. She recalls that she mixed the product in a bucket, and some of the product may have splashed onto her leg(s). She developed a rash on her leg shortly after this exposure that she assumed was poison ivy. Then, she experienced tingling down her leg that she cannot get rid of. Her doctor told her that she had nerve damage. She had a hip and knee replaced and thought that may help the symptoms, but it didn't. Caller has accepted that there is nerve damage, but she is wondering if it could be due to this possible exposure.
019862 - 00012	6/2/2008	MN	071995-00032	ROUNDUP WEED & GRASS KILLER READY TO USE	103601	MODERATE	Caller states her 5 year old has had a reoccurring spider like rash on areas of his skin for about 1 month. Mother notices the rash after he has been

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							playing outside. The mother is worried that it could be due to the Roundup Weed and Grass Killer Ready To Use that her husband sprayed weeks ago. Her son was not around the area when it was sprayed or while it was still wet. The rash comes and goes and does not bother her son. No itching noted.
019862 - 00013	6/10/2008	MO	071995-00032	ROUNDUP WEED & GRASS KILLER READY TO USE	103601	MODERATE	An emergency department physician was calling, about a 68 year old male that presents with a history of sudden onset nausea and ataxia. No vomiting noted. The man stated that he had been spraying weeds with Roundup earlier today but does not think he got any of the product on his skin. The physician states she will be admitting the man for further workup to try and determine the cause of the symptoms.
019862 - 00015	6/8/2008	GA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he applied an unknown formulation of Roundup about a month or so ago while wearing gloves but short sleeves. It may have been windy, and the back spray may have gotten onto the exposed areas of his arms. Caller noticed red blotches from his wrists to his elbows shortly after applying the Roundup. The areas are not raised and they do not itch or hurt. He never recalls his arms being wet with the Roundup. He has been applying Cortisone 10 to both arms with no improvement. Caller has an appointment for MD to look at his arms tomorrow.
019862 - 00016	6/15/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he sprayed Roundup Concentrate (unknown exact formulation) that was diluted 3 ounces to 1 gallon of water. A day or two later he pulled up the grass that he had sprayed. Immediately afterwards, he developed blotches and hives on his arms and trunk. He has been to the emergency room twice for treatment of hives and pruritis. He was given prednisone 10 mg the first time and hydroxyzine the second time. The emergency room didn't believe that his signs and symptoms were related to the Roundup, but rather that he was having an allergic reaction to something.

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019862 - 00017	6/21/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Physician Assistant calling about a 38 year old female that came to the Emergency Department with complaints of malaise, weakness and appeared in poor health. She is jaundiced with acute onset hepatitis. Symptoms started four days earlier. The woman was working in her yard and mixed an unknown Roundup product and an Ortho Weed B Gone product together with her hands. She washed her hands later after she worked in the yard. The woman has associated her illness with this exposure. The attending MD and Physician Assistant do not think either product has anything to do with the woman's illness, but they wanted to double check possible toxicity. The woman is going to be admitted to the ICU.
019877 - 00001	6/1/2008	SHARPSBURG, GA		ROUND-UP 1.33 GALLON WEED KILLER WITH "PULL 'N SPRAY" FEATURE	103601	Unknown or No Effects	A 45 year old male was sprayed directly in the face with product. He was using a 1.33 Gallon container of Round-Up weed killer with a "Pull 'N Spray" delivery system, the pull handle snapped off with the contents under pressure. He got the product in his eyes, nose, and mouth. He does not feel that this product delivery system which is built into the packaging is safe and he believes that it should be considered for recall.
019910 - 00433	5/20/2008	PENNS GROVE, NJ	071995-00008-000239	TOTAL KILL WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller used this product to treat ivy in his yard. Two weeks later his 5 year old son had a seizure for the first time.
019952 - 00001	6/25/2008	IN	034704-00890	MAKAZE	103601	MODERATE	An adult male used the product and thought he may have ingested some of the product through the spray about 3-4 weeks ago. Caller said the product was diluted when he was using it. He has been seeing a MD because he has a heavy spot on his chest like a cough that never goes away. He had an X-ray done and everything was normal.
019978 - 00466	7/22/2008	CA	071995-00008-000239	TOTAL KILL WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	An adult female used the product on the sidewalk. It was windy day and some product got on her arms and legs. Her right hand and leg were in contact with the product. Caller wiped the area with a dry paper towel and did not shower until the

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							next morning. Three days later she broke out in a light fine rash on both her arms and legs. She went to the MD who diagnosed it as an allergic reaction.
020042 - 00001	7/1/2008	IL	071995-00008	ROUNDUP READY-TO-USE WEED & GRASS KILLER	103601	MODERATE	Caller states she inadvertently sprayed Roundup Weed and Grass Killer RTU in her eye and then rinsed for about 5 minutes. She went to the ED for evaluation. She was diagnosed with an abrasion to the right eye and given an analgesic and antibiotic. She had an appt to follow up with her optometrist. The caller was not sure if the pressure from the spray caused the injury or if the sprayer hit her in the eye or just the Roundup.
020043 - 00001	7/1/2008	NY	071995-00020	ROUNDUP CONCENTRATE POISON IVY AND TOUGH BRUSH KILLER 1	103601	MODERATE	Wife calling about her husband who used Roundup Poison Ivy and Tough Brush Killer1 Concentrate that was diluted per label instructions. He also used an Ortho product around the same time. The man showered afterward. He started to feel sick that evening, and was worse the next day with chills, sweating and weakness. He was admitted to the hospital for treatment of pneumonia. The man was very dehydrated on admission. He complained of a severe headache and stomach pains. He had a CT scan of his lungs. Four days later, the physician called from the hospital to state that the man was admitted to the hospital for treatment of pneumonia.
020044 - 00001	7/1/2008	IA	071995-00017	ROUNDUP CONCENTRATE WEED & GRASS KILLER	103601	MODERATE	A 55 year old male was calling about his ongoing occupational dermal and inhalational exposure to Roundup Weed and Grass Killer Concentrate for three months. He complains of vertigo.
020048 - 00001	6/1/2008	MN	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	About one month ago a 52 year old female stated while outside treating weeds with an unspecified Roundup product, her hand had turned brown in color immediately after a dermal exposure to the product.
020065 - 00007	6/30/2008	HOT SPRINGS, AR	062719-00517	ACCORD XRT	103601	MODERATE	Caller is a company rep calling for an MD that is treating a patient that was using these three products in conjunction around 24 hour ago. Caller is not certain about the details of the exposure. Pt. was presenting with SOB and other symptoms, which the caller is unsure of. MD is inquiring

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							about the products. Pt. is currently being treated. Two days later, the patient's symptoms had resolved and he was back at work. It is unclear what the doctor's assessment revealed.
020083 - 00001	8/6/2008	CA	071995-00023	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	103601	MODERATE	Caller states a Roundup Ready to Use product was sprayed in his face and eyes while he was trying to adjust a clogged hose on the spray container. Man rinsed his eyes with water but did not elaborate on the method used. He complains that his left eye is still burning and the vision is blurred. On follow up, the man did rinse his eyes with water a little longer and then went to see his doctor who checked his eye and noted a small burn on the corneal surface. He was prescribed an ointment to use but he does not know its name. The doctor will follow up with him in 4-5 days.
020085 - 00001	7/1/2008	FL	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller states that about a month ago she was weeding with her sister and her sister was spraying Round Up Ready to Use. The caller began to have a burning sensation to her eye and at the time she was not sure if it was sweat in her eye or Round Up. She did go inside and wash off her face and then place a warm compress to her eye. No irrigation done at the time. The caller has been dealing with eye issues since that time. The caller reports that her eyes are red and tearing constantly. She first went to her PMD who prescribed antibiotic eye drops. Those drops did not work and she went to an ophthalmologist who prescribed prednisone for her eyes. That did not work and she has seen an allergist who prescribed eye drops which have also not resolved her symptoms.
020087 - 00001	6/1/2008	IL	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	
020089 - 00001	8/22/2008	MO	071995-00007-059144	ELIMINATOR W & G KILLER SUPER CONCENTRATE	103601	MODERATE	Caller states her yard was sprayed with diluted Eliminator Super Concentrate on Friday morning. Later that day, her child was playing out in yard and could have accessed the area sprayed but it is not confirmed. The child became delusional and

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							hallucinated 30 minutes after playing outside. She was evaluated in the emergency department where a CT scan was done. Drug screens were all negative.
020090 - 00001	7/1/2008	OK	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states the rock area around her flowerbeds was sprayed with Roundup by lawn workers about 1.5 months ago. About an hour after spraying she walked on the rocks to access her hose while wearing socks and tennis shoes. When she turned on the hose, her feet got wet from the water. Worked in the yard for about an hour and then showered with soap and water. About 2 days later her foot broke out into a rash. The urgent care told her it was a topic dermatitis or eczema and a steroid cream was prescribed and used. She followed up with her PMD who referred her to the dermatologist because her symptoms were worsening. The dermatologist scraped the area and diagnosed her with a fungus infection.
020091 - 00001	7/1/2008	MO	000524-00475	GLY-41 HERBICIDE	103601	MODERATE	Caller states that about a month ago he had his arms emerged into a sprayer tank with the diluted Gly-41 product to unclog the sprayer. He did wash up immediately after the exposure but he began to have diarrhea soon after the exposure and he is still having it (symptoms persisting one month).
020092 - 00001	8/1/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Woman calling that was spraying unknown formulation of Roundup Herbicide Concentrate when the sprayer cap came off and sprayed her in the face and eyes. She took a shower and rinsed her eyes for about 30 minutes as they were stinging and burning. She is still having a burning sensation and hazy vision at the time of the call. The eye is not tearing. The next morning, the woman states she had rinsed her eye with well water for approximately one hour last evening just to be sure it was adequately rinsed. This morning she notes a foreign body sensation. The woman states she also got some of the product in her mouth yesterday which resulted in a bitter taste that has now gone away. On follow up, the woman states her MD discovered a small scratch on her cornea

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							and was given eye medications.
020111 - 00245	8/1/2008	MI	071995-00027-000239	BASIC SOLUTIONS WEED AND GRASS KILLER	103601	MODERATE	A 48 year old female reports that her landlord applied product in yard 3 wks ago. Caller walked barefoot in the yard 2. 5 wks after the product had been applied. That night, caller felt exhausted, developed a migraine headache, itchy eyes, palms and feet were red and itchy (BSA 6%). She developed hives and bleeding with development of scabs on her eyelids. She continued to have insomnia for the past 4 nights. Caller's symptoms have nearly subsided by scrubbing her skin daily with soap and water. She did not seek medical treatment by a physician.
020180 - 00018	4/25/2008	GARDEN GROVE, CA	000524-00445	ROUNDUP READY-TO-USE HERBICIDE (UNSPECIFIED)	103601	MAJOR	A fifty-five (55) year old male allegedly deliberately ingested approximately I 00 milliliters of "Roundup Ready To Use" herbicide, and an unknown amount of acetaminophen with the intent to commit suicide.
020180 - 00023	5/16/2008	FONTANA, CA	000524-00445	ROUNDUP	103601	MODERATE	A twenty-three (23) year old male allegedly was exposed to a "Roundup" product when a sudden gust of wind blew the pesticide onto him, causing skin exposure and inhalation. He was applying it to residential landscape plants on a property in Fontana as part of his father's company's maintenance gardener service. He soon experienced symptoms of dizziness, shivering, weakness, flushing, diarrhea, and later became feverish. The victim drove himself to Pomona Valley Medical Center that evening since it was closer to his home and he was admitted overnight.
020222 - 00001	8/1/2008	IA	000524-00536	ROUNDUP POWERMAX	103601	MODERATE	Caller states, about a month ago he was wearing rubber gloves when he had gotten Roundup Powermax Concentrate poured inside of the glove. The caller states that the concentrate sat in contact with his skin for 2-3 minutes. He did wash the skin off very well at that time. Over the past three weeks, the caller has developed arthritis-like symptoms of his hands.
020223 - 00001	7/1/2008	GA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	A 78 year old female sprayed a lot of Roundup Herbicide, unknown dilution or whether or not it was a ready to use product. She may have inhaled a

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							lot of it. The woman had a sore throat around the time of using the product and now has a chronic cough.
020322 - 00001	10/1/2008	IN	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller states an eight year old child got some Roundup Ready to Use spritzed into his right eye. They have rinsed his eye for about five minutes. The caller is asking if they should they go to the ED. On follow up, the child had been taken to the ED and was diagnosed with a small corneal abrasion per fluorescein stain. The evaluating physician stated the abrasion was not related to the Roundup.
020324 - 00001	9/1/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	A caller sprayed her rose bushes for bugs with malathion. She thinks maybe the wind blew some of the spray back onto her skin. Two weeks later, she went to her PMD with the symptom of a rash on her chin. She has returned to her physician three times and has taken three different pills for her symptoms. She called the malathion people, who thought maybe the symptoms may have been caused by Roundup and was given this number to inquire. The caller had used a sprayer that at some time in the past might have held a Roundup product and then had been rinsed prior to use with malathion. She doesn't really think her symptoms are related to the Roundup. The rash had gone away, but at the time of the call on 1 0/15/08 the symptoms have reappeared.
020326 - 00001	8/1/2008	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states approximately 2 months ago he was using a backpack sprayer at work with an unknown formulation of Roundup Herbicide. It leaked all over his back. He didn't notice that it had leaked and kept working all day long using the backpack sprayer. He did not wash until that evening. He used the backpack sprayer on two more occasions. That day his skin became very hot, a rash developed which comes and goes and itches. Sometimes, his body is numb.
020546 - 00001	8/1/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller's son complained to her last month that he had been feeling ill for some time. Son mentioned that he sprayed some Roundup on plants in his

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							backyard 4 months ago. Caller does not know the type of Roundup that was sprayed or the type of exposure that her son had. Son complained of blurred vision and gastrointestinal problems, sleeping a lot, urinating a lot and blood in stools. He saw a PMD to have medical tests for diabetes which was negative.
020550 - 00001	1/1/2009	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Wife calls to say her husband used Roundup to kill weeds and Triazicide to kill ants about 15 minutes ago. He came inside to eat dinner and approximately 5 to 7 minutes later he had symptoms of his peripheral vision becoming dark; telling his wife he could not see. The wife has rinsed his eye and is wondering if either product caused his symptoms. He may have gotten symptoms from the mist of the product but he has no recollection of the product in his eyes. No direct spray to the eye.
020586 - 00001	1/1/2009	FL	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	An adult male used the Roundup product about 3 to 4 weeks ago. He got it on his hands and has been battling a rash and cracking of skin on the hands. He has been using a product called Lac Hydril cream on his hands without much help. He saw his physician 2 days ago and was prescribed clobetasol cream. On follow up, 4 days later, the rash was improving but seemed to worsen at times. The man had been using Vaseline on his hands along with the clobetasol cream and wearing rubber gloves which seemed to make his symptoms worse. On subsequent follow up, a female family member reports that the man's hands continue to improve greatly. The rash is almost gone. He has been using the clobetasol cream and keeping his hands open to air.
020588 - 00001	5/1/2008	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	An adult male was exposed numerous times spraying fence lines last spring and summer. The man is a part-time farmer and was using a backpack sprayer. The man states he planted corn and then after planting went through the field and fence line with Roundup ready corn. Caller states he has also used a termite control product. The man

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							has been to 8 different physicians to resolve a skin issue. The man states the rash has involved his entire body. The rash moves around, one day it is on his torso and then 2 weeks later it goes to another area. He states his skin welts after scratching. He states he has had constant pain, itching and burning for the past 8 to 10 months. The caller has taken many medications and used topical products with no help.
020638 - 00001	3/1/2009	CA	000524-00343	AQUAMASTER	103601	MODERATE	Caller was riding his bike up and down a hill. The parks service was spraying Aqua Master on the side of the road with a tractor to the right of him. He felt a mist on his face, which tingled a bit. He also thought maybe his face felt numb temporarily. This has subsided. He also got a terrible taste in his mouth. The taste persists despite this happening about 3 hours ago. About 20 minutes after the exposure, he noticed, tremors in his right hand, which have subsided.
020639 - 00001	3/1/2009	TX	071995-00025	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	103601	MODERATE	Caller used Roundup about 5.5 hours prior to calling. She first used a brush to apply before diluting and got some on her hands. She then used the sprayer and got some more on her hands. She did wash off after using the product. The caller also took a vicodin for shoulder pain, which she has taken before, at about the same time as the use of the Roundup. Woman is calling now because she felt faint earlier. She now has vision changes and is jittery. No dermal symptoms.
020725 - 00031	12/2/2008	CA		HONCHO	103601	MODERATE	A 47 (forty-seven) year old male, was exposed to a herbicide and an insecticide (U.S. EPA registration numbers unknown) while he was applying them. He experienced weakness, dizziness, and trouble swallowing and was admitted to the hospital. He was later released two days later. He had been applying and handling pesticides for the last four years without proper pesticide training. In addition, he was not provided with the correct and/or appropriate personal protective equipment at the time of the pesticide exposure.
020770 -	3/25/2009	LAKEPORT, CA	071995-	ROUNDUP WEED	103601	MODERATE	An adult female had post application exposure to

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00001			00025	& GRASS KILLER SUPER CONCENTRATE			the product (applied by gardeners). She experienced rash, cough and brown spots on her skin. She was in bed for three days detoxing with pectin and sulfur glutathione nasal wash.
020795 - 00001	4/1/2009	NC	071995-00023	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	103601	MODERATE	An adult male mixed product with water and used a pressurized sprayer that malfunctioned, sprayed him in the face, and got the product in his eyes. He then splashed water into his eyes. Several hours later he was still having redness, slight periorbital edema, and discomfort to the eye. He didn't irrigate more than a of couple minutes. He had irrigated his eyes but for a short amount of time but 3.5 hours later he was still complaining of irritation, tearing and some crusting of drainage. The ED MD just looked at his eye visually, no instruments were used. The MD said there was a burn and an infection in both eyes. Antibiotic drops were prescribed.
020796 - 00001	4/13/2009	NV	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller states he used Roundup Ready to Use about 30 minutes ago, when the wind blew some mist back into his face and he accidently inhaled some. Caller states he is having nausea, difficulty breathing, feels short of breath, no vomiting. Caller states he does have a history of COPD. On follow up, the man states he is still having difficulty breathing and stated he had a seizure. Man states he has a history of a seizure disorder. On follow up with the ED after several unsuccessful attempts earlier, the RN states the man had a low dilantin level. He did not have any respiratory symptoms and did not require any breathing treatments. The RN states the man is in the ED frequently and was discharged to home several hours ago.
020800 - 00001	4/5/2009	VA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	A 30 year old adult male suicide attempt (ingested approximately 3oz).
020802 - 00001	4/16/2009	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he used Roundup Concentrate extensively on his property about 2 weeks ago. He mixed it according to the package directions. The man states it had sprinkled rain at least once since he had applied the Roundup. Yesterday, he was digging fence posts in a gravel-like bed where he

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							had previously sprayed the Roundup. It was very windy. The man was wearing boots, gloves, long sleeved shirt and long pants. He noticed his hands were itching and he went in and washed his hands. He states his feet began itching and then he went into 'shock.' The man's wife called an ambulance and he was taken to an ED. He was treated with Benadryl and other "anti allergy stuff' and given intravenous fluids. The man states the physician could find no reason for his symptoms. No bite or sting was noted. The man was discharged to home and now is asymptomatic.
020803 - 00001	4/16/2009	OR	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states she is a first responder from Oregon state calling about herself and her neighbor. Today, the street was sprayed with a combination of 3 herbicides, Glyphosate (Buccaneer), Milestone from Dow chemical and Spyder which contains 'Sulfometuron methyl (applied from a helicopter). She is also concerned about her neighbor that takes Cyclobenzaprine, asking if the chemicals could be interacting with his medication. The caller states she has also been exposed to the same chemicals since she lives on the same street. She has a history of liver disease. The neighbor refuses to go MD or the hospital. The neighbor has a severe headache 'left sided in occipital area with 'brain swelling', 'mastoid swelling neck', and muscle spasms. Onset of symptoms was 2-3 days ago, sometimes he tells her 2-3 weeks ago. The caller states she has had muscle tremors, hot and cold flashes, chills, occipital headache, mastoid swelling, and headache since last week. She states her heart was irregular a couple of days ago.
020813 - 00177	4/17/2009	LITTLE SILVER, NJ	071995-00008-000239	TOTAL KILL WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	A 4 year old male sprayed the product. It was unclear if the child had any exposure to the product. The next day, the child woke up with swollen eyes. He went to MD and was prescribed a steroidal ointment. Two days later he was greatly improved.
020875 - 00002	5/1/2009	NC	071995-00032	ROUNDUP WEED & GRASS KILLER	103601	MODERATE	Caller states 8 year old walked in front of a spray of Roundup Ready to Use Weed and Grass Killer

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				READY-TO-USE			2% about 24 hours ago. He was instructed to go inside and wash it off but evidently did not because he developed rash and itching later. Mother called back several hours later to report that the child developed hives on his legs, abdomen, back and upper arms. He was also started on a new medication last week which he stopped due to a stomach virus but restarted today. The child was evaluated by his pediatrician who administered an antihistamine injection. The MD thought the symptoms may be related to a post viral reaction. Child to follow up with his pediatrician.
020875 - 00003	5/1/2009	NJ	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller states that she was using Roundup Ready to Use yesterday and got some of the foam on the back of her hand. She did not think much about it and just wiped off the Roundup instead of washing it off. She reports within a few hours of the exposure, she began to feel tremendously dizzy. She is able to monitor her blood pressure and it was 225/101 mmhg.
020875 - 00005	5/1/2009	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Ophthalmologist calling about a woman that got an unknown formulation of a Roundup concentrate in her eye yesterday. Unknown if immediate first aid provided or not. The eye was diagnosed as having an acid burn with minor corneal staining. Artificial tears recommended. The woman was discharged to home.
020875 - 00006	5/1/2009	NY	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Son calling from the ED with his father being evaluated for sudden onset of short term memory loss and sharp pain in his head. He sprayed Roundup this morning and then at 4 pm, he was talking with a neighbor and all of a sudden didn't remember anything and had a sharp pain in his head. He sprayed the product normally, with no significant exposure. They are currently in an ED, waiting for the MD to evaluate him.
020988 - 00001	7/12/2009	KS	004787-00023	GLYFOS X-TRA HERBICIDE	103601	MODERATE	Caller's husband had been spraying diluted Glyfos X-TRA Herbicide and started to develop flu-like symptoms, fever and chills the next day. Patient sought medical care and was prescribed

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							azithromycin and propoxyphene. According to patient, the medications were not working.
020997 - 00031	6/6/2009	AR	000239-02637	GROUNDCLEAR VEGETATION KILLER CONCENTRATE	103601	MODERATE	A 55 year old male sprayed the diluted product along the driveway and fence. He was wearing shorts. Two days later he developed knee to ankle petechia rash with edema and cellulitis developing. CNP thinks it is a combination product and sun exposure. He was given Prednisone and 2 Decadron injections. He went back to MD because he developed fever/chills/rash/bumps that are now itchy and raised. He was treated with Benadryl and an inhaler for a previous condition. He was also prescribed lincocin.
021052 - 00001	6/1/2009	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states, a few days ago, she became very lethargic and felt like she couldn't get enough oxygen. Her cat also had been sick recently. The caller states she had gone to run an errand and noticed some blue stuff on the ground near where she lives. She called the state department and was told that the product was Roundup.
021060 - 00001	6/1/2009	MS	071995-00017	ROUNDUP CONCENTRATE WEED & GRASS KILLER 1	103601	MODERATE	Caller states he sprayed over 1 gallon of Roundup. It is questionable whether his shirt was damp from the overspray. Caller states it was hot outside. He states there was some overspray on his feet. While spraying, caller states he had a burning spot on his neck which stopped burning when he washed it off. He took a shower 3-4 hours after application. The next day, he woke up itching, a rash on his hands, arms and feet (not like poison ivy) and welts all over him. He had a boiled lobster look. He took Benadryl 25 mg which resolved the symptoms.
021064 - 00001	6/28/2009	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states her 36 year old son had a seizure at church on Sunday 6-28-09. The day before, on Saturday, he sprayed Roundup using a backpack sprayer. It was a windy day. Unknown if any mist blew onto his skin.
021065 - 00001	1/1/2009	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states, for the past year he has had atypical seizure disorder. He is wondering if it could be caused by his exposure to Roundup Weed and Grass Killer. He typically used a 41% glyphosate formulation and diluted it according to directions.

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							He doesn't recall a specific exposure to the chemical. He states he is just trying to rule out causes for his seizures.
021191 - 00021	8/4/2009	IL	000239-02637	GROUNDCLEAR TRIOX TOTAL VEGETATION KILLER 1	103601	MODERATE	An adult male used the product. While he was spraying the hose on his sprayer broke and it sprayed all over his skin. He stated he did wash initially, but now has an infection in his mouth. He has seen a dentist and is being treated. The dentist is not sure of cause of infection.
021244 - 00001	6/1/2009	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller used a Roundup Weed and Grass Killer Pull and Spray product at least 2 months ago. He was spraying around plants. He thought he was sweating, but apparently the sprayer was leaking onto his hand. He did not realize this until after he was done spraying. Since then, he has gotten huge blisters on his hands. He says they are as large as a thumb. He says they're so deep that you can see the muscle. He has been to the doctor and the doctor gave him 2 pills to take, but the pills didn't help. The doctor didn't tell him what was wrong with his hands.
021245 - 00001	8/1/2009	MA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller reports, a neighbor sprayed Roundup unknown concentration diluted 3 ounces to 1 gallon of water, on poison ivy outside the front of her home, approximately 5 yards away. Her windows were open. Within an hour she reports becoming dizzy, experienced a headache unrelieved by ibuprofen, a little relief with aspirin, nausea, shakiness and trembling. Symptoms are better if she lies flat. "Something wrong with her head and spinal cord". She was finally better and then her neighbor sprayed again 6 days later, and the symptoms have started all over again. She feels fine when she is lying down but the symptoms return when she gets up. She denies mishaps or any direct contact with the product.
021247 - 00001	8/1/2009	NC	071995-00032	ROUNDUP WEED AND GRASS KILLER READY TO USE	103601	MODERATE	Caller states that she had been spraying Roundup Ready to Use yesterday and had left the bottle sit on the front porch. At some point, she found her 2 year old grandson with the bottle and he had been spraying the Roundup. He was spitting out acting

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							like there was a bad taste in his mouth at that time. Caller was not concerned at the time but the child woke up with symptom of shaking badly last night at 0300. He is currently sleeping now and has an appointment with his PMD this afternoon.
021250 - 00001	8/1/2009	DE	071995-00023	ROUNDUP WEED & GRASS KILLER 1 READY TO USE	103601	MAJOR	Caller states his 88 year old mother is in the hospital with kidney problems. The son is calling to see if Roundup could be a factor in her illness. He states that in the last 6 months, his mom has used 4 containers of the Roundup Weed and Grass Killer Ready to Use. No actual ingestion, nor dermal exposure. The son is concerned that she may have inhaled some.
021251 - 00001	8/1/2009	MS	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states sometime yesterday, his 5 year old son must have gotten near some Roundup. No further history of any actual exposure available. Child may also have gotten some trash and dirt in his eye this morning while playing outside. This morning, the child's eye was swollen and painful so he couldn't open it. Dad took to him to the emergency department and they diagnosed a big scratch on one eye and prescribed hydrocortisone drops. Now this evening, the child's other eye is painful and swollen. Dad has given an over the counter analgesic and put the child to bed.
021252 - 00001	8/1/2009	SC	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states her spouse was sick with a high fever, dehydration and confusion last week. He is better now. He had good care by the doctor. She states he uses Roundup a lot but is unaware of any specific exposure.
021254 - 00001	7/1/2009	VA	071995-00008	ROUNDUP READY TO USE WEED AND GRASS KILLER	103601	MODERATE	Caller used Roundup in high weeds for 2 days. About two weeks later, he developed a bumpy, itchy rash all over his legs and arms. Approximately a month later, the rash is on his back. No mishaps with the product. He does not recall becoming wet with the product. He has seen a dermatologist for treatment and has had biopsies done. He has been taken off all his medications except his antihypertensive.
021256 - 00001	7/1/2009	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller believes her neighbor upstairs is using Roundup and Miracle Gro. She states she was

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							outside while the neighbor was spraying the other day but denies dermal contact. She is suffering from hoarseness, dizziness, light headedness and skin burning sensation.
021397 - 00001	9/1/2009	CA	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY TO USE	103601	MODERATE	Spouse got Roundup Weed and Grass Killer Ready to Use on his skin. He had on shorts and flip flops. He denies mishaps or spills but was walking thru the weeded area he had treated. No recall of being wet with the product. He suspects he showered the next day. A few days later, he developed a biting sensation on his ankles and feet. At first, he attributed the symptom to insect bites, and started wearing soaks and used mosquito spray. The symptoms worsened and he developed tiny bumps and tiny fluid filled blisters that looked like herpes on the back of his hands. The symptoms then progressed to the dorsum of feet. About 6-7 weeks later, the rash is generalized all over his arms, legs, trunk, buttocks and hands with itchy, weeping blisters and bumps. He saw a dermatologist, who was not sure what it was. The caller mentioned Roundup and she told him that was likely the cause. He has a prescription for a steroid dose pack but had not used it. He is using topical steroids.
021398 - 00001	9/1/2009	WA	071995-00025	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	103601	MAJOR	Call from an emergency crew on scene where an 84 year old male drank Roundup Weed and Grass Killer Super Concentrate approximately 20 minutes prior. His wife found him in the garage when he told her he had intentionally drunk from the 35 ounce container which is now almost one third gone. They estimate 6 ounces ingested;
021401 - 00001	10/1/2009	TN	071995-00032	ROUNDUP WEED AND GRASS KILLER READY TO USE	103601	MODERATE	Caller states that a month or so ago, he was turning the selector nozzle on Roundup Ready to Use when a small amount of the foam got on the corner of his eye. The eyelid, only, was exposed. He remembered thinking that he should wash that off when he was done but he may or may not have rinsed it. About a day later, he began to have a minor itch at the exposed site and peeling skin

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							from that area. Both symptoms persist to today. He has applied hydrocortisone cream to the area maybe once or twice.
021466 - 00001	11/1/2009	ND	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller stated he used a concentrate Roundup Weed Killer for farming, trying to kill trees. He is unsure how it was diluted. He had a typical overspray exposure, and showered at the end of the day. Two days later, he got out of bed and fell. He was seen in the emergency department and was diagnosed as having Guillain-Barre. He went to the Mayo Clinic, 2 months ago, and was told his symptoms are consistent with Guillain-Barre. He is still having muscle weakness in his legs.
021610 - 00001	1/23/2010	HI	000524-00475	ROUNDUP PRO	103601	DEATH	49 yr. old Hawaiian man intentionally ingested Roundup Pro, death. ER staff said there was nothing they could do
021635 - 00001	9/1/2009	NJ	071995-00025	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	103601	MODERATE	Caller states about 4 months ago some diluted Roundup Weed and Grass Killer Super Concentrate splashed on his leg when he was applying the product. He did not wash it off until later when he started having burning and stinging on his legs. He has been to two different dermatologists and his PMD over the past 4 months and has been given three different creams that have not gotten rid of the burning sensation. The symptom is still present off and on.
021635 - 00002	11/1/2009	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states she sprayed weeds with an unknown type of Roundup less than 2 months ago. She used one glove for pulling weeds that were sprayed with the Roundup and then folded her arms while talking to neighbors. She developed a rash on the upper arm area several days later and the rash has remained since then. She is under the care of a dermatologist who cannot say what the cause is. The area is red now. It started as a mosquito bite like nodule, hard boil, and dime size bumps under her skin. She never had any blistery rash.
021817 - 00001	3/23/2010	CA	000524-00445	ROUNDUP HERBICIDE FROM MONSANTO	103601	MODERATE	Caller states that about one month ago, her gardener applied an unknown formulation of Roundup from a golf course to her weeds outside. Her small dog was outside running in that area the

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							next day and developed small pinpoint lesions on its face which seemed to bother the dog by itching. After holding the dog, she too has developed pinpoint bumps with craters in them, which are extremely pruritic on her arms. She has seen a dermatologist and they have done biopsies which are pending.
021819 - 00001	3/6/2009	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states, in the spring a year ago, she was using a Roundup product at work. Some went onto her pant leg and into her sock. Some went onto her ankle which she wiped off with a wet paper towel and soap soon afterwards. Since then she has had an intermittent rash on her ankle that gets dark when she scratches it. She has consulted her PMD.
021898 - 00001	4/9/2010	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller used a Roundup product 2 weeks ago. She got some into her eye and it burned, so she flushed it for 1-2 minutes with water. Seven days ago, she noticed large floaters in her eye. She contacted her PMD, who told her to see an eye doctor immediately, but she didn't. Today, she has thousands of black spots that she sees. Caller states symptom came on suddenly. Eyes feel dry and hurt.
021899 - 00001	3/26/2010	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states she used Roundup more than 1 month ago. She vaguely remembers a drip getting onto her hand or wrist area. She doesn't think she washed it off right away because it was such a minimal amount. For several weeks, she has had an area on the top of her wrist that is a patch of bumps that resembles poison ivy and weeps a yellowy discharge. It itches and appears to be gradually getter larger. It started out looking like 4-5 bug bites, but it has progressively gotten worse. She is going to MD next week.
021900 - 00001	4/15/2010	CO	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY TO USE	103601	MODERATE	Ophthalmologist is seeing a 39 year old male with a complaint of pupil dilation in one eye only. In trying to determine the cause, the man reports using Roundup Weed and Grass Killer Ready to Use, four days ago. He is not aware of getting any in his eyes, but states it might have blown there.

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							No complaint of eye irritation or redness at the time of use.
021902 - 00001	3/24/2010	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller notes that several weeks ago she was using Roundup concentrate (6 ounces to 1 gallon) dilution and then also mixed it (12 oz to 1 gallon). Some was sprayed on her hands and legs when her sprayer got clogged. She has been noticing muscle spasms to her hands, feet, and legs and urinary incontinence.
021983 - 00001	5/15/2010	MO	042750-00061-072693	CROP SURE GLYPHOSATE PLUS	103601	MODERATE	An adult male indicates he was exposed to the product 2 weeks ago. He was sitting on an ATV seat saturated with diluted product. He reports he developed a severe rash all over my body. He saw a doctor and was placed on the oral antibiotic doxycycline. The caller also reports he had developed diarrhea for three days following the dermal exposure described. The caller is ASX at this point.
021983 - 00002	5/24/2010	IL	042750-00061-072693	CROP SMART GLYPHOSATE 41 PLUS	103601	MODERATE	An adult male states that product spilled on his leg one week ago. Two days ago his wife noticed some swelling in his lower legs.
021990 - 00001	5/9/2010	AZ	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY-TO-USE	103601	MODERATE	Caller states that he got Roundup Ready to Use (unknown formulation) on him this past January (approximately 4 months ago). It sprayed on him when he opened the container. Caller states he has had symptoms of numbness and swelling of tongue and lack of taste since the exposure.
021991 - 00001	5/14/2010	TX	000524-00454	HONCHO PLUS HERBICIDE	103601	MODERATE	Man works at a tractor supply store and has become sensitive to some chemicals he works with at the job. Last evening, he was mixing Honcho Plus around 6-6:30 pm, getting the concentrate on his hands while mixing. He did rinse with water promptly and later with soap and water. He did feel burning on his hands at the point of contact but no rash or redness noted after rinsing with water. Around 10 pm when his spouse saw him at home, he was disoriented and confused, she brought him to the local ER.
021992 - 00001	5/11/2010	MO	071995-00017	ROUNDUP CONCENTRATE WEED AND	103601	MODERATE	Man sprayed Roundup on his property today. No known exposure. Tonight he is having significant symptoms but refuses to be checked out at the ED.

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				GRASS KILLER 1			He has symptoms of dizziness, walking into walls, drowsiness, and ataxia.
021993 - 00001	5/5/2010	OH	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY-TO-USE	103601	MODERATE	Caller used a Roundup Ready to Use product, 2 days ago in her yard. No mishaps during use. Yesterday, she was working in her yard in the area she had sprayed the day prior and noticed her hand was itching. Then the back of her neck, and legs broke out. She has generalized hives, swelling and itching. She is concerned she came in contact with the Roundup and worried that it is causing her symptoms.
021994 - 00001	5/28/2010	MO	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY-TO-USE	103601	MODERATE	Woman used Roundup Weed and Grass Killer Ready to Use 2 days ago, getting some on her hands and spilling some on her feet while pouring it from one container to another. The smell of the product makes her feel lightheaded. She did wash well but did not feel well later in the day, becoming nauseated and continued to be nauseated. She was at the dentist office yesterday. She had her BP checked at 83/58. Today, her fingertips are numb. She denies history of medical problems. She did not ingest any Roundup.
022100 - 00001	6/19/2010	HI	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Call from Hawaii at a hardware store where 2 days ago, a weed killer that was in a sprayer device was returned to the store. It was evidently sprayed on the arm of an employee at that time. She did not get to wash it off right away but rinsed a few minutes later. She states the customer told her it contained Roundup, but there was no way to verify what was in the container. The employee complains of a red, flushed look to her arm and leg (leg was not sprayed). She feels a funny tingling type sensation to the skin, and complains of chest pain and shortness of breath.
022101 - 00001	6/18/2010	OH	071995-00032	ROUNDUP WEED AND GRASS KILLER - READY TO USE	103601	MODERATE	Caller states, 2 days ago her friend sprayed Roundup Ready to Use on some very tall weeds. The day after spraying, she started to have trouble breathing and can hardly walk now, without becoming winded. The friend thinks that she may have breathed in some of the mist while spraying the Roundup.

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022102 - 00001	6/30/2010	NY	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	Call coming from Syracuse EMS and they are en route to a home where an adult male is unconscious and has been reportedly using Roundup all day. No other details are known, caller wants to know what type of herbicide is in the Roundup and if it would cause this type of symptom.
022103 - 00001	6/24/2010	MO	000524-00454	BUCCANEER PLUS HERBICIDE	103601	MODERATE	Caller states she was spraying with Buccaneer Plus about May 25th in her yard. It was diluted to label directions. She sprayed for about 3 hours then came in and took a shower. The day before she knew she had been around poison ivy and started itching. MD prescribed her Prednisone. Since then, she has seen MD about 4 times. She says her skin is swollen from head to toe for one week. Her skin appeared to be turning orange from a burn, the past 4 days, with some skin peeling. MD asked her if she was exposed to herbicides and is treating her now with Bactrim to 'get poison out of her '.On follow up the nurse practitioner stated she did not feel the woman's symptoms were related to the Buccaneer Plus.
022175 - 00002	7/8/2010	ALTOONA, PA	053883-00059	SURRENDER ERASER SYSTEMIC WEED & GRASS KILLER	103601	MODERATE	A 17 year old male sprayed this product outdoors using a backpack sprayer for about 3 hrs. He was not wearing any PPE, just shorts and a t-shirt. Some of the product spilled down the back of his shirt. He showered that night as usual, but woke up the following morning with 'flu-like symptoms' as well as some muscle and joint pain. No fever or other symptoms. Although he was "80% better," three days later he saw his MD. No specific treatment was rendered at that time as he was getting better on his own.
022192 - 00002	7/28/2010		000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states her husband was spraying Roundup concentrate. The wind was blowing while spraying. She found her husband lying on the grass. She got him inside and he took a shower. His nose is congested.
022192 - 00003	7/17/2010	MO	071995-00018	ROUNDUP WEED AND GRASS KILLER 1-SUPER CONCENTRATE	103601	MODERATE	Woman presents to the ER with a complaint of numbness to both legs and difficulty urinating. She is able to go only small amounts since Wednesday. The RN believes, on Wednesday, the woman was

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							using Roundup concentrate that she had diluted and got some on her feet. There are few details of the exposure. The woman denies using any other chemicals.
022192 - 00005	7/20/2010	CT	071995-00023	ROUNDUP READY TO USE POISON IVY AND TOUGH BRUSH KILLER 3	103601	MODERATE	Caller states he spilled some Roundup Ready to Use Poison Ivy and Tough Brush Killer 3 on his thumb about 30 minutes ago. At the time of exposure, he used hand sanitizer to rub it off. About 10 minutes later, he washed with water and soap for 5-10 minutes. He notes some redness on his skin just below his wrist but not on his thumb at the point of contact. He states he feels tingling of the hand and is dizzy. On follow up, the man stated he was at the emergency room because he was short of breath and felt like he was going to pass out from being dizzy. He states his tongue went white and his mouth was dry.
022192 - 00007	7/1/2010	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller and her sister are elderly. They have an absentee landlord neighbor whose lot adjoins theirs. In the middle part of April, he sprayed the grass between their homes. They began having symptoms at that time. Symptoms experienced were, sore throat with "pus sacs" and red pimples down the throat, burning sensation in the skin and coming up out of the esophagus, abdominal cramping, vomiting, itching, hair loss and headaches. Their MD gave them a Z pack antibiotic, and eventually they were doing all right. On the 24th of May they saw the neighbor out spraying and then leaving. They felt stinging of their eyes and skin, respiratory irritation, dizziness at the time of spraying. They got another Z pack antibiotic from PMD afterwards.
022193 - 00002	1/1/2010	KAUNAKAKAI, MOLOKAI, HI		ROUNDUP	103601	C,MODERATE	Roundup sprayed near female AA member: malaise, sinus discharge, Part vague: mentions death nearby after Roundup was used
022193 - 00003	11/1/2009	MOLOKAI, HI		ROUNDUP	103601	DEATH	Roundup sprayed near female AA member: malaise, sinus discharge, Part vague: mentions death nearby after Roundup was used
022268 - 00001	8/30/2010	VA	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	Caller states her sister-in -law drank a pint of Roundup - unknown formulation yesterday. The

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							woman was out on pass from a psychiatric center and when she returned she was vomiting.
022270 - 00001	8/2/2010	IL	071995-00032	ROUNDUP WEED AND GRASS KILLER-READY TO USE	103601	MODERATE	Woman spraying the Roundup Ready to Use this afternoon and thinks that she got some on her hand and then rubbed it into her eye. Tonight, her eye is very irritated and is lachrymating. Woman has removed her contact lens. On follow up the next morning, the woman went to her eye doctor early in the morning and was diagnosed with severe chemical burn to the cornea. The doctor prescribed antibiotics. It was noted that at the time of the exposure, the caller had no burning sensation or irritation.
022271 - 00001	8/31/2010	VA	071995-00032	ROUNDUP WEED AND GRASS KILLER-READY TO USE	103601	MODERATE	Caller states that his father was using Roundup Ready to Use yesterday and got some of the spray in his hair. He did shampoo his hair soon after the exposure. At some point he was reading a newspaper and has a habit of licking his finger to help turn the page. When he licked his finger he noted immediately the left side of his tongue went very numb. He woke up this morning with left sided facial drooping and his left eyelid is drooping.
022272 - 00014	7/22/2010	DE	071995-00008-000239	TOTAL KILL WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	An adult female got some of this on her legs. Then 2 days later she developed blisters on her leg. She thought it was just poison ivy. She used a steroid cream on her symptoms and the blisters went away. Then it turned into a big bubble so she went to MD and they gave Death oral steroids. She now has scars on her leg. She was calling to see if it might be related to the product.
022395 - 00001	9/17/2010	FL	071995-00025	ROUNDUP WEED AND GRASS KILLER SUPER CONCENTRATE	103601	MODERATE	An adult male had mixed a total of 15 gallons using Roundup Super Concentrate, dilution of 3 ounces of concentrate per gallon of water to apply over 15 acres. He has a large container on the back of his pickup truck and he used a sprayer hose to spray the Roundup. There was an occasional wind shift and he got the product mist on his skin. He was spraying for approximately 6 hours. He had hives that started in the groin area. His feet began to itch and then he had welts all over. He was

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							treated with Benadryl and had an appointment with his MD the next day.
022401 - 00001	9/1/2010	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Wife calling after being prompted by nurse to question pesticide encephalopathy. Her husband used Roundup 4 days ago. The son brought the product over stating it is Roundup in a spray bottle. The caller does not have the label, ingredients or dilution available. Her husband eyes were swollen the day after use. His symptoms have progressively gotten worse. He started with a headache, now he is disoriented with hallucinations, left arm and leg numbness. The caller has taken her spouse to the hospital 3 times. All CT scans do not show sign of stroke. Her husband's PA just keeps sending them back to the hospital. The man does not take any maintenance medications.
022453 - 00001	10/6/2010	TN	071995-00032	ROUNDUP WEED AND GRASS KILLER-READY TO USE	103601	MODERATE	Caller states that his wife was helping him spray Roundup Ready to Use about 4 weeks ago. She was holding up a sheet of tin foil that they were using to shield plants that they did not want sprayed. No known exposure to the Roundup at that time. Three to four days later, she started with symptoms of a rash on her chest, which has spread to her face. They have gone to their PMD and since have been referred to a dermatologist. She is on Prednisone and various creams. Biopsy of the rash was done this week.
022454 - 00001	########	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Ace Hardware employee calling on behalf of a customer who got a mist of an unknown formulation of Roundup in his face about 20 minutes ago. He has developed chest pressure.
022504 - 00001	11/8/2010	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Physician office calling about a man that has been using diluted Roundup every day for 3 months while wearing gloves but sometimes touches his face. His skin is red and swollen with blisters.
022805 - 00001	10/1/2010	OH	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY-TO-USE	103601	MODERATE	Woman calling in regards to an indirect exposure to a Roundup Weed and Grass Killer product. She had used the product indoors to treat and is now calling due to the eruption of red raised lesion to the back of her leg which occurred following exposure and had then spread to her neck, arms as

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							well as her waist. The caller stated that she has been in to see dermatology and was given steroid injections which essentially eradicated the condition with only an occasional outbreak. Now she is calling just in case the rash may be related.
022938 - 00002	4/14/2011	PR	000524-00475	ROUNDUP ULTRA	103601	MODERATE	Caller is from Puerto Rico. Spanish translator conferenced on the line. The translator states the caller used Roundup Ultra 2 months ago. He got a spray of the diluted product on his forearm. Since that time, he has been nauseated and had a burning stomach. No oral ingestion. No rashes noted post exposure. No chest symptoms. He has seen a cardiologist. He would like to know what to take to fix these symptoms. MRPC discussed the product toxicity. The symptoms do not correlate with the expected response to the product. Advised to continue under the care of his PMD. MRPC is available to speak to the MD if desired.
022938 - 00004	4/15/2011	NE	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states his 14 year old gardener sprayed Roundup last week and broke out in hives from head to toe that evening. The teen had used it all last summer with no reaction. MRPC discussed the product toxicity. The symptom does not correlate with the expected response to the product. Advised to have the family or MD contact MRPC if further concerns.
022938 - 00005	4/15/2011	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Son calling, about his 70 year old father who accidently drank less than a mouthful of Roundup about a week ago. The father thinks he spit most of it out. The caller states that they are taking him to the hospital tonight because he is still having symptoms. The caller does not know what the specific product was. He knows that it was a diluted concentrate. The caller states his father's gums and the top of his mouth are sore and painful. His father has been seen once before today. The physician told him that he had 'pus pockets' in his mouth. He also had areas of irritation in his mouth that were bleeding. His father is now complaining that his stomach is hurting. MRPC discussed the product toxicity.

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							Delayed onset abdominal pain is not an expected response to the product. Advised to observe for worsening of symptoms. On follow up, spoke with the daughter-in-law. The man is in the hospital. Running some tests. The MD thinks it may be some sort of chemical burn. PCC is available to provide information about the active ingredient or consult if the MD desires. No return calls received.
022938 - 00006	4/20/2011	TN	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY TO USE	103601	MODERATE	Caller states that on 3/11/11, he was spraying a Roundup Ready to Use product. He felt liquid on his right thigh through his work jeans. He washed the area within 30 minutes. 5 days later he had chills, different muscle twitches. His twitches are mostly gone and his chills are resolved. Now he has a burning sensation at the site for less then a week. The caller is unable to find the ingredients on the label he had saved. MRPC discussed the product toxicity. The symptoms do not correspond with expected response to the product. Advised to follow up with PMD if his symptoms persist or worsen.
022938 - 00007	2/1/2011	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Mother of a 27 year old female notes that she believes her daughter's ex-husband may have been poisoning her with Roundup. The last contact with him would have been February and no contact with him since then. The woman states that they have been researching different things and she may have been poisoned by a concentrated type of product. Ate food twice prior to February that tasted strange. MD is involved and not sure of what was ingested or if it is a poisoning or medical problem. Also notes other products such as WD40 come up missing from the home. She complains of hives, mouth burning, stomach upset, poor PO intake, vomiting, diarrhea, and blue nails.
022938 - 00008	4/28/2011	GA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Dad calls about 11 year old daughter who lost some vision in one eye. She is currently in CT scan for evaluation of the eye now. Caller states about a week or 2 earlier, he had sprayed the ground with diluted Roundup. This past Monday night and today, his daughter had planted some flowers. She

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							may have rubbed her eye with her hand. He is asking if that could affect her vision. MRPC discussed the product toxicity. The symptoms do not correspond with expected response to the product. SPI concerned re: possible misinterpretation of symptoms and/or possible misidentification of product or mixed exposure.
023018 - 00001	5/21/2011	CA	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY TO USE	103601	MODERATE	Caller states that she already had a pre-existing case of productive bronchitis. On this past Wednesday, when she sprayed about 3/4th of a gallon of Roundup Ready to Use formulation, her bronchitis turned into wheezing. She did a nebulization treatment that she had in her home. After doing a treatment with no improvement she involved her PMD and is now hospitalized. Her breathing status has gotten worse.
023018 - 00005	5/2/2011	GA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states his brother had been spraying Roundup outside earlier today and ' had a seizure' about an hour ago. No history of seizures before. No product known to be on skin or ingested. The man had diarrhea, a seizure and fell in the bathroom.
023052 - 00001	6/3/2011	TN	000524-00454	HONCHO PLUS HERBICIDE	103601	MODERATE	One month ago, the man was spraying an apple tree using a water mixture of Honcho Plus. He got some overspray on his head and was not wearing a hat that day. He has a raised itchy rash on his scalp. He saw his doctor today who recommended he cut his hair short and recommended a topical treatment. On follow up, 3 days later, the man states, he used hydrocortisone cream as directed. It has helped the itching but the raised bumps are still there. His doctor diagnosed them as seborrheic dermatitis and that he should cut his hair short for it to get better. The Honcho Plus probably did not cause this.
023052 - 00002	6/6/2011	HI	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller is concerned about her brother who uses Roundup and was just diagnosed with bone marrow cancer. Caller questions if benzene is in Roundup
023052 - 00005	6/22/2011	PA	000524-00454-	GLY-4 PLUS HERBICIDE	103601	MODERATE	Caller states she was misted with water diluted Gly -4 Plus Roundup when she was on a tractor

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			072693				mowing a neighbor's lawn and man went by spraying at distance away, of a semi-tractor trailer. She could feel the mist on her body and can still see it on her sunglasses that she had on that day. She started to cough and her throat was burning. She stopped and went inside and rinsed out her mouth. She went to an ER that night because she could not stop coughing. She was told she was being treated for chemical burns to her throat and lungs. She was given nebulizer treatments, flovent, albuterol, diphenhydramine x 2 Q 4 hours and steroids. Two days later, she got on the same mower and within 5 minutes the symptoms developed again and she was treated in the ER. About 5 weeks later, she is doing better but her throat is still sore. No known allergies or history of asthma.
023052 - 00006	6/23/2011	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states her spouse was exposed to the spray of Roundup when the wind shifted during spraying about 1 year ago. No mask was worn. He has had problems with his breathing and nose bleeds since then. The man bathed after the exposure. He had diluted the Roundup- 2 quarts in 25 gallons of water. Since that time he has had bronchitis. 15 days later he had a nose bleed that bled 5-6 times/day for over a week. The man has a long standing history of nose bleeds since childhood. The ENT MD performed a cauterization. He remained flat on his back for several weeks using nasal gel and antibiotics. About 6-7 wks ago, the man became ill and went to the MD and was given levaquin for treatment of pneumonia, although his lungs were clear. He got better, when the levaquin ran out, his symptoms got worse. He was given prednisone and cough syrup for bronchospasms. His lungs are clear per CXR. When the steroid was gone he got worse again. He is now seeing a pulmonary specialist and given more antibiotics and now has a fever.
023177 - 00001	7/18/2011	CA	000524-00475	ROUNDUP PRO	103601	MODERATE	Caller states he was spraying for approximately 1 week with diluted Roundup Pro. The wind was

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							blowing, but he did not feel he got any on him. He wore a mask while spraying. He went to the MD for an earache but there was no ear infection. Complaint of a headache and some ataxia.
023183 - 00001	7/2/2011	CO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states 80 year old male who used Roundup yesterday was exposed dermally to the mist. The man did not wash the area with soap and water. The man is experiencing nausea, stomach cramps and chest pain.
023208 - 00001	7/27/2011	TX	071995-00023	ROUNDUP WEED & GRASS KILLER 1 READY TO USE	103601	MODERATE	Caller states she used Roundup Weed and Grass Killer Ready to Use yesterday. The woman states it was very hot and she was sweating a lot. She used a handkerchief to wipe her face. Her eyes started to burn and continued after closing her eyes. She instilled natural tears. Today, she is having trouble seeing, particularly out of one part of her eye. On follow up, the woman states she went to the ophthalmologist, who says she has a scratch on each eye. She has a prescription for erythromycin drops, and one for Tobradex. Her vision was improved.
023262 - 00001	8/23/2011	NC	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 - READY TO USE	103601	MODERATE	Caller states he used Roundup that 'kills poison ivy ' one month ago on some weeds by his home. He states it has rained 3 times fairly hard since that application. Every time he gets out of his car and walks by this area, he states his nose and throat bums. The man called back again for the phone number to the company to inquire how to remove the product from the air. The man called back later, stating he continues to have eye and throat burning in spite of having several hard rains in his area. He states that he can hardly breathe and just feels 'sick'. Unable to name details other than he feels sick. The caller has not phoned his physician or the product line as recommended previously.
023265 - 00001	8/2/2011	IL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that an unknown formulation of Roundup was sprayed on a weeded area and a bush area in his apartment complex for 2 days in a row. The caller states when he steps outside the door he's affected. He has had no direct exposure to the

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							Roundup, but he walks by the sprayed areas. He states he cannot get the MSDS from the complex. No air conditioning in the apartment. The caller has a history of epilepsy and is a smoker. He states he has been having seizures everyday since the spraying. He is losing his appetite and has lost 6 pounds since last Thursday. When he spits, blood comes out of his esophagus. The caller states when he does not go on the property, he is fine.
023266 - 00001	8/15/2011	MN	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller is calling on behalf of her father-in-law. He used Roundup on July 9th. Since then, he started experiencing tingling of his hands, arms, feet and lightheadedness. He keeps touching skin and saying it looks different. The caller cannot see a change in her father-in-law's skin. The man has been evaluated for heavy metals and toxins. His doctor could not find anything wrong with him or no medical cause of these symptoms and advised the man to call the poison center. A CAT scan and MRI and artery testing revealed nothing. The man also seems lethargic and quiet when he used to be full of life. To the caller's knowledge, the man put concentrate in another bottle and added water. He sprayed it in cracks of the sidewalk, around the pool shed. The wind was blowing, so any exposure would have just been from overspray. He showered that day, but it could have been hours after spraying.
023267 - 00001	8/21/2011	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	ER calling about 22 year old male that arrived by EMS and states he ingested 2 mouthfuls of an unknown formulation of Roundup that was in soda bottle where he is staying about 24 hours prior. Apparently, the man had no complaints until tonight. His tongue is white without ulcerations; the nurse says it looks like thrush on the tongue. His pupils were large, no history of vomiting or diarrhea. En route to ER, EMS reported the man to be posturing and foaming at the mouth. One liter of LR given IV. The man is talking nonstop "all over the place" at this time. The man was admitted to the HCF for seizure precautions and monitoring.

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							Labs were within normal limits. He had a complaint of his throat being sore and also reported that he did vomit twice but unknown when he actually vomited. The next day the man had no further complaints, stable vital signs, no GLC symptoms or seizure activity.
023361 - 00001	6/22/2011	WA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that 3 months ago, a lawn care company sprayed an unknown Roundup product on his lawn. A day or a few days later, he worked in the yard on his knees. Later, he thought, he must have had the product soak up through his pants because he developed a blister on his knee. He called his PMD and dermatologist immediately, who were both booked up solid. He went to the pharmacy where they recommended hydrocortisone cream, which he has been using since that time. Symptoms of blistered swollen knee, extending to the waist is present. No itching is noted.
023364 - 00001	9/24/2011	AZ	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	man intentionally drank 150-350 ml concentrated Roundup Herbicide with vodka; he was found and taken to ER; hypotension requiring vasopressors which resulted in increased lactate leading to metabolic acidosis, evidence of renal impairment. Man showed signs of improvement by day 4 post exposure.
023365 - 00001	9/12/2010	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Man calling is 44 years old, with a history of a traumatic brain injury in 2006 which has resulted in balance and equilibrium issues. He has difficulty walking which has worsened over the last year with increasing muscle spasms to the point he can no longer walk. His symptoms are similar to those of MS. He recently learned that the marijuana he had smoked 8 to 12 months ago had been killed with Roundup.
023531 - 00001	6/14/2011	NM	000524-00517	RANGER PRO	103601	MODERATE	Nurse practitioner calling from a PMD office where a 67 year old male is being seen for the third time in the recent past. He has been using Ranger Pro 8 to1 0 times between 3 to 5 months ago. The last time he used the product was about 3 months ago. He dilutes the product 5 ounces into 1 gallon.

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							He did get the diluted product on his ankle 5 months ago. He was wearing shoes (not sandals) with no socks. He did not wash off until the next day with his normal morning shower. He had a stripe of redness on the top of his left foot and developed joint pain of his left ankle. Since that time he has had hives on his right forearm, a red raised rash of his axilla area. He has been on a medrol dose pack.
023532 - 00001	########	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states his 82 year old dad was mixing one of the concentrate Roundup products with water 6 months ago and spilled some on his finger but did not wash it off right away. Unknown if he spilled the concentrate or the dilution on his finger. Blisters appeared on the finger but the caller does not know the time frame of onset. Since then, he has had a burning pain in the finger. The skin is now completely normal.
023577 - 00001	8/6/2011	NEW ORLEANS, LA	042750-00061	GLY STAR PLUS	103601	MINOR	An adult male got the product in his eye. He experienced vision problems. He went to three MDs. He was not able to resolve his symptoms.
023628 - 00001	########	BROKEN BOW, OK	042750-00060	GLY STAR ORIGINAL	103601	MODERATE	An adult male got the product in his eye. He experienced vision problems.
023704 - 00001	12/8/2011	CAPE CORAL, FL	042750-00061	GLY STAR PRO	103601	MINOR	An adult male go the product on his hands. He did not rinse his skin right away. His skin became dried and cracked.
023710 - 00001	1/23/2011	WV	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Woman calls from West Virginia about her exposure to an unknown formulation of Roundup one year ago. She was sitting on Main Street on a windy day when she noticed a misting on her face and skin. At the same time, the railroad was applying Roundup to the weeded areas on their property. She came home and called the railroad office to see what they were using and was told 'Roundup' but no particular formulation. She feels she was 'heavily sprayed' but showered within 1-2 hrs of the exposure when she got home. The only concern she offers is that her skin seems like it was 'burned' in several places and has been peeling.
023821 - 00001	10/1/2011	MI	000524-00445	ROUNDUP ORIGINAL	103601	MODERATE	5 crew members were in a field in MI doing a survey project. The field was adjacent to a farm. A

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							contractor sprayed 2 fields next to workers with roundup. Workers had multiple symptoms. Headache, nausea, burning of eyes, nose, throat, metallic taste in mouth. Decontaminated within 1 hour of exposure. Symptoms resolved 1.5 hours after decontamination.
023906 - 00001	3/31/2012	IN	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he was spraying an unknown formulation of Roundup that was diluted to a stronger strength than what is instructed. The sprayer hose came off and sprayed the product in his mouth, face and eyes an hour ago. He showered and flushed his eyes for 30 minutes. He has rinsed his eyes every 15 minutes since then. His eyes are burning. He drank 2 glasses of chocolate milk. He is calling now because he is dizzy and feels his speech is slurred. Adequate dermal, PO and ocular irrigation were performed.
024028 - 00001	4/21/2012	MO	071995-00023	ROUNDUP WEED & GRASS KILLER 1 READY TO USE	103601	MAJOR	Caller notes that on Monday his wife was out spraying with some type of Roundup Ready To Use. It spilled and made the back of her shirt wet. On Friday, they found out that she experienced a miscarriage. The caller is asking if this was related to her exposure on Monday.
024028 - 00002	4/20/2012	MO	071995-00023	ROUNDUP WEED & GRASS KILLER 1 READY TO USE	103601	MODERATE	Caller states this past Tuesday afternoon, his wife began to have involuntary movements of her left arm and leg, which now looks as if it is moving to her right side, and her speech and thought process were altered. The caller phoned her PMD who referred her into an ED and she was admitted to the hospital. She has had a stroke work up, CT scan and MRI. The caller is inquiring about the use of Roundup.
024172 - 00001	5/18/2012	OK	071995-00016	ROUNDUP SURE SHOT FOAM	103601	MODERATE	Caller states she used a whole container of Roundup Sure Shot Foam last evening on the weeds when some came back on her. She did not think much of it and did not take a shower until later that night. She has used Roundup in the past without any problems. The caller is covered with hives from her waist to her knees. No trouble swallowing and no swelling. MRPC discussed the product toxicity. Possible allergic reaction to an

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							ingredient if the woman is hypersensitive. The woman is planning on going to the ER for treatment. She does not have any Benadryl at home. On follow up, the woman was taking Benadryl and applied Caladryl. The woman is feeling better and her symptoms are improving. Woman states it was a windy day and she may have inhaled some of the mist.
024172 - 00003	5/17/2012	MD	071995-00032	ROUNDUP READY TO USE POISON IVY AND TOUGH BRUSH KILLER 2	103601	MODERATE	Man calling to rule out all causes of his symptoms of shortness of breath and nausea that he has experienced for the past 1 week. He has been to the ER and the symptoms are non cardiac related. Last week, he used an old bottle of Roundup Poison Ivy and Brush Killer RTU formula. The bottle was in the garage for a few years. The sprayer leaked and got on his hands and arms for 5 minutes only. He washed off promptly. MRPC discussed the product toxicity. The symptoms do not correlate with the expected response to the product.
024172 - 00007	5/16/2012	ID	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Ophthalmologist calling with vague details. He is seeing an adult male, who got Roundup splashed into an eye a couple of days ago. Unsure of the exact Roundup product or if a concentrate or diluted formulation. He is unsure if there was even an ocular exposure to Roundup. No irrigation done by the man at the time of the exposure. His eyelid is very swollen and part of his cornea has come off. MRPC discussed the product toxicity. The symptom does not correspond with the expected response to the product. Caller declined to have the product information faxed to him or to give information on the person that was exposed.
024172 - 00008	5/21/2012	IA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that her husband had been spraying an unknown formulation of diluted professional Roundup on the farm this past Thursday. He got some on his hands and did not wash if off for about 5 minutes. On Thursday evening into Friday morning he began to have tightness of his chest and he broke out into hives. He went to the ED and had a cardiac work up which was negative. He took Benadryl for the hives and they dissipated. Today

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							he started with the hives again and in addition he is having swelling of his hands and feet. MRPC discussed the product toxicity. The symptoms do not correspond with the expected response to the product. Advised to stay under medical care of MD.
024172 - 00009	5/30/2012	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	RN calling from ER about a farmer, who had been spraying with an unknown formulation of Roundup for a couple of hours about 3.5 hours ago. Afterwards, he was talking to a friend, and started having slurred speech and according to his friend, he seemed to "zone out for a minute". RN states since arrival to the ER, the man has been awake and alert, oriented x 3, vital signs have been stable and within normal limits. No slurred speech noted. MRPC discussed the product toxicity. The symptoms are not consistent with the expected response to the product. The man was discharged to home within a few hours of arrival.
024222 - 00001	4/25/2012	PR	000869-00238	GREEN LIGHT COM-PLEET 41% SYSTEMIC GRASS & WEED KILLER 2	103601	MODERATE	A male used the product and experienced an all over body rash. He was seen by a medical facility and subsequently was treated the rash. The medical facility advised the rash would go away and the caller should have no lasting effects from the rash. Caller wanting to know if this is truthful information from the medical center. One week later he still had the rash.
024294 - 00004	6/5/2012	MO	000524-00454	BUCCANEER PLUS HERBICIDE	103601	MODERATE	Caller used Buccaneer Plus yesterday that he mixed in a 30 gallon sprayer to pull behind his lawnmower. He mixed 1/2 gallon of the solution in 25 gallons of water. No mishaps, although may have been exposed to some of the overspray. He does not recall significant wetness of his skin or clothes from the Buccaneer. He also burned a citronella type candle in his home last night. He broke out in hives last night with mild itching. He took a Loratadine 10 mg tablet earlier today.
024294 - 00005	6/20/2012	TX	000524-00475	ROUNDUP PRO	103601	MODERATE	Nurse calling from an occupational clinic about a 44 year old male who had an exposure to diluted Roundup Pro 30 minutes ago. The man was getting ready to use his rig he had prepared 2 days prior for

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							spraying. It had Roundup Pro inside the tank diluted 34 oz to 55 gallons of water. He went to turn it on and the hose popped off and sprayed him in his face, eyes and chest area. He had safety goggles on. They have been rinsing his eyes for 15 minutes. He is complaining of a skin burning sensation and throat irritation. On follow up, the nurse states the man complains of slight blurring of vision. On further follow up, it was noted that the man had a corneal abrasion. He was given eye drops and discharged to home.
024309 - 00002	6/18/2012	OROVILLE, CA	042750-00061-002217	PRONTO BIG N' TUF	103601	MODERATE	A 47 year old male was exposed to product and symptoms (dizziness, vertigo, coughing, choking) started that evening. The product was sprayed into ground, he then shoveled the dirt and may have inhaled dust and also had dermal exposure
024371 - 00001	7/13/2012	IL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states a family member has been sick for about a week with breathing problems. He has been to the hospital and had prednisone and other drugs prescribed without improvement. COPD was diagnosed. The man has had some breathing issues in the past, but his symptoms got worse suddenly and quickly. About a week or two ago, the man accidentally got an unknown concentrate Roundup, diluted for use, on his skin. It splashed over the front of him and his face. He took a shower immediately. His symptoms began about one week later. No known cough or choke at the time and no other symptoms noted at the time of the exposure.
024372 - 00001	7/10/2012	TN	000524-00529	ROUNDUP PRO CONCENTRATE HERBICIDE	103601	MODERATE	Man calling with a concern about a Roundup exposure. About 2 months ago, he sprayed a 2% water dilution of Roundup Pro Concentrate and then was lying on the ground, possibly in the area just sprayed. Shortly after this exposure, the man reports he developed joint and muscle pain enough to warrant going to the doctor.
024486 - 00008	2/5/2009	ST. GABRIEL, LA		ROUNDUP	103601	MAJOR	Exposure to "Roundup" in her employment at Syngenta in St. Gabriel, LA. Child was allegedly born with defects that include developmental and respiratory abnormalities. Date of birth is

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							unknown.
024486 - 00011	8/23/2012	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Woman calling is concerned that her next door neighbor is overusing Roundup used in quantity. She noticed this summer that after he sprays she has an expiratory wheeze. She went to her doctor who prescribed an inhaler that helps. She did not do the spraying nor did she feel any spray mist on her skin when she was out working in her garden when he was spraying. MRPC discussed the product toxicity. The symptom does not correlate with the expected response to the product.
024486 - 00012	8/27/2012	KY	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Man calls with concerns about his neighbor's crop spraying applied liberally by a tractor 4 months ago. He was outside during some of the application exposed because the rpm's were increased on the tractor vaporizing the Roundup making it difficult to avoid exposure. The caller states the neighbor did it on purpose. The caller thinks they used Roundup but the state testing has been inconclusive and was covered up. A state lawyer was involved. He states he feels ~c o'(became sick shortly after starting with constipation, liver problems, sinus infection, gum infection, boils, lost two teeth, woke up with his bones separated in his foot shortly after the spraying. He went to the doctor who felt his back and dental issues are the cause of the problems. The farmer told the state inspectors that Roundup was used. The caller states since he worked with the pipeline in the 1950s and 1960s he probably mixed some other chemicals with it. The man would like to know if there are any antidotes for Roundup poisoning. MRPC discussed the product toxicity. The symptoms are not related to the expected response to the product. Advised to remain under the care of MD.
024486 - 00013	8/29/2012	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	MD calling from the emergency department about a child who spent the day supervised by parents and most of that time was on an ATV. Parents were working on the farm and moving cows. Parents were also spraying weeds with 2,4-D and Roundup.

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							Child did not have any direct contact with the herbicides. Child had unpasteurized milk for the first time as well today. No witnessed ingestions of any plant material and no meds/drugs available. Child presents with a dry mouth, agitation, delirium, nystagmus, HR 150 ST, minor hyperthermia, flushed appearance. MRPC discussed the product toxicity. The symptoms do not correlate with the expected response to the product. Continue with symptomatic care and further history of possible exposure to other substances or medications.
024494 - 00019	8/13/2012	WA	071995-00007-000239	ORTHO TOTAL KILL WEED & GARDEN KILLER CONCENTRATE HERBICIDE	103601	MODERATE	Caller is a physician assistant. He has a patient who was exposed to this product about 40 minutes ago. He complains of pain. Caller reports ocular irritation. He flushed his eyes for only 10 minutes prior to presentation. At this time, P. K., a male patient, is having his eyes flushed again for a longer period of time. Caller has not done a slit lamp exam on this patient yet. After flushing, he will do that and refer to ophthalmology as needed. His eye was irrigated. No damage seen on slit lamp exam. He was prescribed an antibiotic drop. Was then released and comfortable at discharge.
024551 - 00001	9/13/2012	DE	071995-00017	ROUNDUP CONCENTRATE WEED AND GRASS KILLER 1	103601	MODERATE	Caller states she was outside, when her nephew was spraying Roundup, an 18% formulation, that had been diluted. She was near the area being treated when she felt like her throat was closing up. The caller states she is chemically sensitive. About 1.5 weeks later, she noted her eye and the side of her face along her hair line looked scalded. Her eye lid was red and puffy. It would then flake and peel. She had some ocular redness and swelling that has seemed to resolve. She was seen by her PMD and treated with oral steroids. The symptoms resolved but have come back. Now, she is being managed by an ophthalmologist and has been diagnosed with blephritis. She is currently on minocycline orally, but had previously used tobradex to the eye and eyelid. The caller suspects a relationship with the Roundup and wondering

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							what treatment should be considered.
024691 - 00001	8/2/2012	JASPER, AL	001381-00192	CORNERSTONE PLUS	103601	MODERATE	A male farm worker unintentionally drank some Cornerstone Plus that was in a water cooler. He experienced bloody diarrhea and was diagnosed with colitis.
024948 - 00001	1/3/2013	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	The caller wants to know if it is possible for a person to harm himself with Roundup concentrate. Someone has drank some and is unconscious. The caller wants to know if it is possible that Roundup concentrate is the cause.
025087 - 00001	3/19/2013	CO	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	Monsanto/Scott company calling about an older female who has sent an e-mail or letter to the company claiming exposure to Roundup Concentrate has caused Parkinson's disease. The woman stated that her exposure was "dipping her hands in a Roundup solution."
025157 - 00001	4/25/2013	OH	000524-00445	ROUNDUP HERBICIDE	103601	DEATH,MAJOR	An adult female emailed about a study she read on tumors in rats exposed to Roundup. Her husband & a neighbor both died of tumors. She and husband were exposed to Roundup 3 years ago and both developed tumors. She is concerned about her own health. She provided no phone number. Monsanto emailed a response and asked her to contact them but she didn't. Exposure to Roundup is not clear.
025228 - 00001	4/14/2013	CA	000524-00517	RANGER PRO	103601	MODERATE	Caller states that about 30 minutes ago she poured some Ranger Pro Herbicide into a measuring cup for her husband to dilute the product. She started to feel weird and to wheeze. Caller states that more than 20 years ago, she was spraying a Wilson Leather Protectant product and inhaled some resulting in 70% lung capacity and now she seems to be very sensitive to chemical smells. She went inside and used her inhaler and is feeling better.
025233 - 00001	4/26/2013	ID	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he has just put all the pieces of this together, and before he sees a doctor he wants information. He states someone sneaked in during the middle of the night several months ago and poisoned his apricot tree and other trees. He then ate the apricots. He thinks it was a neighbor lady, who has passed away now, but he saw a Roundup container at her house before she departed. He has

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							symptoms of weakness in his lower extremities and numbness to his feet and legs.
025234 - 00001	4/19/2013	GA	042750-00061	GLY STAR PLUS FROM AGRI STAR	103601	MODERATE	Caller states that about a month ago he was using Gly Star Plus and got some of the concentrate on his hands. He rinsed it off right away but then realized the concentrate had been on the handle of the sprayer he was using. Two days after the exposure, he had flu like symptoms, profuse watery diarrhea, nausea, vomiting, and abdominal pain. He now has periods of itching all over and small red bumps noted on his chest. When he sits down and then gets up he gets chills up and down his legs. He has not seen a doctor for his symptoms yet.
025309 - 00001	2/1/2013	KY	071995-00023	ROUNDUP WEED AND GRASS KILLER1 READY TO USE	103601	MODERATE	Caller states she used a ready to use Roundup 3 months ago while wearing shorts. She assumes some of the mist got on her legs. She did not shower afterwards. Two days later, she developed a rash that looked "like bites" or tiny bumps on the front of her legs. She went to her primary MD who gave her an antibiotic and steroid combination cream. She used it, and the rash faded but came right back. It is very pruritic. She went to one dermatologist that she feels was just "guessing" about the rash and has an appointment for next Wednesday with another dermatologist. The caller states she has used Roundup for years and never had a problem until this time.
025312 - 00001	5/1/2013	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that 4 weeks ago, she was riding a cart at a golf course when she got covered with the spray of a Roundup product from a truck that was in front of her. The caller says that she must have inhaled the Roundup, because she has had a cough since that time. Occasionally mucous comes up with the cough. In speaking with the caller, the cough is intermittent. A few times a day she has had a runny nose that pre-dates the exposure. The woman has not sought any evaluation or treatment by a MD.
025314 - 00001	5/14/2013	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that she was exposed to Roundup earlier today around noon time, and is now "very sick". She states that her neighbor sprayed

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							Roundup in her yard to try to kill her. The neighbor told her that she was "a weed that needed to be gotten rid of'. The caller states she inhaled some of the product when she was in her yard as he was spraying it. She thinks her neighbor was using one of the concentrated products, but is not sure exactly which one. The caller complains of throat irritation, palpitations, trouble breathing, and "very sharp" chest pain. On follow up, the woman was observed and monitored for several hours and had been discharged to home.
025315 - 00001	5/22/2013	IN	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that last week her husband used a weed killer. There are three different weed killers in their garage, she is unsure of which product he used. The caller states that her husband is hospitalized with an infection and 2 blood clots in his leg and is concerned that this could be caused by Roundup getting into a cut that he had on his arm while using the weed killer. Unknown the type of infection or if the infection is in his arm wound. He is currently receiving antibiotic therapy.
025316 - 00001	5/26/2013	CO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Man used an unspecified formula of diluted Roundup concentrate for about 2 hours. There was a little wind on that day. He got some on his hands as he mixed it. No accidents during spraying. Denies working with any poison ivy/oak. He showered with soap and water within an hour of finishing his spraying. He has not used Roundup before. No new soaps or foods. The only thing different over the last 3 days is, he has been using his Ventolin HFA inhaler that he was prescribed during a bout with pneumonia this past year. No difficulty breathing or wheezing is reported. The Roundup was mixed 6 ounces to 2 gallons of water. The next day, a raised itchy rash started on bilateral arms, worse on forearms, some on top of hands, on both ankles above his socks, and neck. All these areas of skin were exposed during the use of the product. He has started using topical hydrocortisone cream. On follow up, the man stated after he took a dose

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							of the Benadryl, his itching had resolved and he was feeling well and going back outside to do more yard work. On further follow up, the man said later that evening, he went to the ER for worsening of symptoms. He was advised by the MD to continue taking Benadryl, and was prescribed prednisone and Pepcid. The hives and itching were clearing. He was diagnosed with Urticaria/hives secondary to environmental allergies.
025347 - 00005	3/6/2013	CA		ROUND UP CONCENTRATE	103601	MODERATE	An individual has been hospitalized after drinking Round Up (active ingredient: Glyphosate).The patient stated that he accidently ingested the Round Up Concentrate that was stored in the garage. The patient had purchased the Round Up Concentrate at Home Depot about a month ago and after use stored the remaining pesticide in a V-8 Juice bottle in the garage. He drank out of the V-8 bottle thinking it was juice. Once he realized what he drank was not V-8 Juice, he rinsed his mouth with water and mouthwash but did not tell anyone what had happen since he did not feel any symptoms. At about 7 pm the same day, he began to feel ill with throat pain and told his wife what had happened that morning. The wife transported him to the Kaiser Permanente hospital where he was admitted for treatment.
025424 - 00001	6/17/2013	TX	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Adult female calling about possibly pulling weeds on that her husband had sprayed with Roundup the day before. Her hands were red the evening after pulling the weeds. The next day, her hands were swollen and she developed hives everywhere. She went to the ER and was given steroids and was better. Today, she went back to the ER because of difficulty breathing.
025583 - 00005	7/1/2013	NJ	000524-00445	ROUNDUP	103601	MODERATE	Neighbor sprayed caller's property sometime before the weekend getting an unknown formulation of Roundup on her fig trees. The leaves on the fig are not withered but are not as robust as usual. Family members enjoy the fruit,

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							peeling it before eating. On Saturday, the caller, her adult son, his friend and his friends 6 month pregnant wife helped her cut down the fig tree and carry the plant branches to a dumpster. Of all the 4 people who cleared the fig tree the son's male friend (who is allergic to everything) had bronchospasms for which he needed a breathing treatment in an ER. He was discharged to home and is fine now. It is unconfirmed whether Roundup was actually on the fig tree.
025583 - 00006	7/19/2013	FL	000524-00445	ROUNDUP	103601	MODERATE	Caller states that her neighbor was using a diluted Roundup product in her own sprayer. Something happened with the hose and she ended up getting diluted Roundup into her eye about 20 minutes ago. Prior to calling, she did attempt to irrigate her eye using an eye cup. Her eye is still burning and stinging. On follow up, the woman stated she had a foreign body sensation. She was referred to her ophthalmologist for an eye exam and treatment. She was diagnosed with a corneal burn to the corner of her eye. She was prescribed antibiotic and steroid drops and is scheduled to follow up with the ophthalmologist.
025583 - 00008	7/31/2013	CA	071995-00025	ROUNDUP WEED AND GRASS KILLER SUPER CONCENTRATE	103601	MODERATE	Woman calling regarding herself, stating she has been having "stomach issues" and works with Roundup frequently. She says that she has accidentally drunk some diluted Roundup but her signs and symptoms have been going on for about 3 months now. Caller says that the "cancer meds" she is taking could also be the cause of her symptoms.
025583 - 00009	7/17/2013	IL	071995-00023	ROUNDUP WEED AND GRASS KILLER1 READY TO USE	103601	MODERATE	Caller states 7 4 year old male in good health, was picking weeds, 1 year ago, from a garden not knowing his wife had sprayed with Roundup Ready to Use. He was not wearing gloves but washed his hands after pulling the weeds. Since then, he has had an itching rash on the inside palm of his right hand. It feels tender and is sensitive to touch. "Cold water will irritate". He has been to a few dermatologists and has taken corticosteroids. Recently, he was given Flucanozole in case it is a

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							fungus infection
025583 - 00011	7/1/2012	NJ	000524-00475	ROUNDUP ULTRA	103601	MAJOR	A nurse in New Jersey asked to speak with someone about Roundup Ultra and a strange illness her brother-in-law has had for a year now. She stated that he has a farm and used Roundup Ultra and doctors cannot find anything wrong with him but to say his body may have had an allergic reaction from using the Roundup product. His blood work shows nothing but his body has been swollen and she fears he doesn't have much time left.

Appendix 3

SENSOR-Pesticides 1998-2009 Moderate & High Severity Glyphosate Cases			
Case ID	Year	Severity	Case Description
CA15534	2008	High	Roundup drifted onto officer as he was responding to an accident on the side of the freeway
FL02294	2007	High	45 y/o man was spraying product and hose started leaking and product spilled on both hands. Did not wash immediately.
FL02346	2007	High	Male has been using high yield zawl for almost a month.
FL03304	2009	High	Patient is suspected of trying to commit suicide by ingesting an unknown amount of roundup weed and grass killer concentrate
LA00205	2001	High	mother bought pest. from man in neighborhood; stored in v8 container; mentally ill brother used pest. to make choc. milk
NC01758	2009	High	Man ingested roundup from an antifreeze bottle with beer or wine Caller is EMS has man who has ingested 8-16 oz of Roundup from an antifreeze container and alcohol. He has symptoms of vomiting several times, hypotension, blood pressure drop, acidotic, respiratory arrest apnea, has developed wide complex tachycardia. His prior medical history is negative.
CA02204	1998	Moderate	Not Available
CA03535	1998	Moderate	Not Available
CA03640	1998	Moderate	Not Available
CA03704	1998	Moderate	Not Available
CA04445	1999	Moderate	Not Available
CA05234	1999	Moderate	Not Available
CA05260	1998	Moderate	Not Available
CA05563	1999	Moderate	Not Available
CA06363	1999	Moderate	Not Available
CA07993	2000	Moderate	Not Available
CA09242	2001	Moderate	Not Available
CA09383	2001	Moderate	Not Available
CA09779	2001	Moderate	Not Available
CA10137	2002	Moderate	Not Available
CA11225	2002	Moderate	Not Available
CA13383	2003	Moderate	Not Available
CA13488	2003	Moderate	Not Available
CA14027	2004	Moderate	He used a new weed spray and broke out in rashes the next morning
CA14187	2002	Moderate	Works spraying chemicals, now has a rash
CA14302	2005	Moderate	Round-up got in both eyes
CA14626	2006	Moderate	Developed red burning marks and blisters on his chest, back, and arm after using chemicals at work.
CA15535	2008	Moderate	Wearing a backpack sprayer and it leaked

SENSOR-Pesticides 1998-2009 Moderate & High Severity Glyphosate Cases			
Case ID	Year	Severity	Case Description
CA15626	2008	Moderate	Hose malfunctioned and leather gloves were soaked with glyphosate
CA15644	2008	Moderate	The hose of a sprayer broke and splashed his face/eyes
CA15707	2008	Moderate	Confused, mixed roundup with soda and drank it
CA15957	2008	Moderate	Backpack sprayer leaked
FL00379	1998	Moderate	While applying glyphosate, complainant cut her arm on a tree branch. The chemical irritated and burned the cut tissue.
FL00621	1999	Moderate	Dockworker alleges pesticide drifted onto him after a pesticide application. He was neck deep in water at the time.
FL01328	2004	Moderate	Neighbor applied pesticide at fence line. Residents were exposed and got ill.
FL01531	2006	Moderate	26y/o male admits to ing approx 8oz of Round up concentrate plus weed/grass killer
FL01588	2006	Moderate	Patient worked with chemical for a few days at high levels. Not wearing protective gear.
FL01671	2006	Moderate	Patient was exposed to open container of round-up at work
FL01930	2006	Moderate	Patient was spraying round up in his yard and got some in his eyes.
FL02292	2007	Moderate	9 year old was sprayed in eye by a herbicide.
FL02375	2007	Moderate	Landscaper was exposed to glyphosate to days ago.
FL02521	2007	Moderate	Male was working on yard and spraying product. Some product got on hands.
FL03631	2009	Moderate	Not Available
LA00998	2003	Moderate	Drift from aerial application to sugar cane field behind home. Plane was spraying Polado herbicide (glyphosate) Walking in yard and noticed an aerial application to sugar cane field behind home. SX of headache, SOB, eye irritation, and abdominal pain. Complainant called sheriff and was taken to ER for treatment.
LA01692	2005	Moderate	Got round up in eyes at work; cleaning tank; backsplash into face and eyes
LA02721	2007	Moderate	mixed (clorox + roundup concentrate plus weed and grass killer)then spilled on arm; dermal irritation
LA03061	2008	Moderate	child at aunt's house yesterday was sprayed in face with (maxide ready-to-use grass and weed killer)
MI00036	2001	Moderate	working in field, spraying roundup, when wind shifted. Sprayed on field, unknown type of sprayer.

SENSOR-Pesticides 1998-2009 Moderate & High Severity Glyphosate Cases			
Case ID	Year	Severity	Case Description
MI00276	2003	Moderate	Mixture of pesticides spilled in storage room. He has history of industrial asthma & when he walked by, could not breathe.
MI00397	2005	Moderate	Farm exposure to mixture of roundup, ammonium sulfate, & liquid nitrogen. Flushed eyes & arm before going to ED.
MI00583	2005	Moderate	Was trying to unclog pump, got some spray in her eye. Rinsed with hose at work.
MI01980	2009	Moderate	Not Available
NC00086	2007	Moderate	Woman purposefully ingested Roundup at home. 30 year old woman intentionally ingested Roundup Brushkiller Concentrate on 04/19/2007. Somebody from her house called Poison Control. The patient started vomiting and had a strong abdominal pain. She was taken to a nearby hospital and was admitted to the critical care unit. According to surveillance program records, the patient was still in hospital on 04/20/2007 but her condition was improved.
NY00313	2000	Moderate	Woman was working in her garden using a pump bottle of ready-to-use Roundup herbicide. Woman was working in her garden using a pump bottle of ready to use Roundup Lawn & Grass herbicide. She did not follow instructions & was not wearing protective clothing, eye wear or gloves. She states that she was sprayed as there was a drift wind and also she states that the trigger pump was leaking down her hand & wrist.
OR01583	2007	Moderate	Splashed glyphosate in both eyes after turning on high-pressure hose.
TX01850	2000	Moderate	Case is a farmworker/licensed pesticide applicator and had been spraying round-up near cotton fields for approximately 2 week
TX02115	2000	Moderate	Case mixes and applies round-up daily as part of job on ranch. Wears no protection and contact is common. Developed painful
TX04618	2005	Moderate	Case was putting bottle of roundup on top shelf, bottle fell over splashing case in face & eyes.
TX05736	2008	Moderate	case exposed to herbicide at work while spraying weeds and brush along a city road; wind caused spray to blow back at him.
WA00936	2002	Moderate	40 y/o female employee of Walmart reported a skin rash/irritation following contact with a herbicide. She was stocking the shelves when exposed. About 9 days later she sought medical attention.
WA01571	2004	Moderate	A 43 y/o female was applying an herbicide and was sprayed in the right eye from a cracked nozzle assembly. She washed with running water for 10-15 minutes and still developed ocular pain. She sought medical attention the same day.
WA02644	2007	Moderate	A 21 y/o male landscaper worker, according to medical records, inhaled fumes while spraying plants. He developed symptoms and presented at clinic with respiratory, G.I., cardiovascular, neurological and dermal symptoms one day after exposure. He was treated and released, returning again to clinic next day. Patient was lost to follow-up and employer did not supply spray records as requested.

SENSOR-Pesticides 1998-2009 Moderate & High Severity Glyphosate Cases			
Case ID	Year	Severity	Case Description
WA03234	2009	Moderate	A 40 y/o male tractor driver developed respiratory symptoms and eye irritation after he drove the tractor disking soil in the vineyard behind a boom sprayer applying herbicide. The tractor driver wore a face mask. He went to the emergency department and continued to seek medical care afterwards for asthma-like symptoms. He had a history of environmental allergies but no prior history of asthma. The herbicide was applied to the vineyard eleven times over a 5-week period.

Appendix 4

Glyphosate: Literature Review Methodology

To identify the epidemiological investigations of the association between glyphosate exposure and adverse health effects, we queried PubMed/Medline and the Institute of Scientific Information's Web of Science. We also performed limited searches using Google.Scholar. Querying these three search engines is considered a comprehensive way to identify relevant articles (Falagas, 2008). PubMed is the most commonly used biomedical search engine used by researchers today, however Web of Science offers similar journal coverage in addition to citation mapping capabilities. We performed citation mapping using Web of Science, examining key articles which referenced the articles included in the literature review, to identify additional relevant material. We also sought relevant articles through Googel.Scholar. These methods are discussed herein.

We generated the following search strings. Emphasis was placed upon identification of all possible epidemiological studies available, and the ability to use the identical search string in both PubMed/Medline and Web of Science. Regarding Google.Scholar, we attempted use of similar search strings as well as the advanced search capabilities available [http://scholar.google.com/advanced_scholar_search?hl=en&as_sdt=20000].
The search strings are found below:

> PubMed: (((Glyphosate[tw] OR (N-(phosphonomethyl)glycine[tw]) OR gliphosate[tw] OR Roundup[tw] OR yerbimat[tw] OR (glyphosate hydrochloride (2:1)[tw]) AND (humans[tw] AND (epidemiologic studies[tw] OR cohort*[tw] OR case control[tw] OR cross section*[tw] OR cluster*[tw] OR environmental exposure*[tw] OR occupational exposure*[tw] OR ecologic stud*[tw] OR aggregate stud*[tw])))
> Web of Science: ((((Glyphosate OR (N-(phosphonomethyl)glycine) OR gliphosate OR Roundup OR yerbimat OR (glyphosate hydrochloride (2:1))) AND human AND (epidemiologic stud* OR cohort* OR case control OR cross section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud*))))

We did not restrict the date of publication; however with a few exceptions most studies identified were published 1990-present. After elimination of duplicate references between the two search engines, we identified 90 research articles of potential interest. For inclusion in this review, articles were published in English language, analytic epidemiologic investigation, and included a glyphosate risk estimate. Among the 59 articles excluded from review at this point in the search process, 12 were evaluation of human exposure only, 16 related to an acute pesticide poisoning incident(s), 8 articles concerned evaluation of ecological exposure (non-human) only, 7 were experimental toxicological studies and 6 were review articles or editorials (not original research) or did not meet inclusion criteria for other reasons. Therefore, there were 31 full-text original epidemiological research articles of an association between glyphosate exposure and an adverse human health outcomes included in full-text review, and 10 were included in the HED review. There were 21 articles excluded as a result of full-text review (14 exposure-only, no epidemiological risk assessment; 6 review articles; and 1 toxicological study).

Citation mapping included review of two high-quality summary articles of the investigation into glyphosate toxicity in the human population (Mink et al., 2011; Pamela J. Mink, Jack S. Mandel, Bonnielin K. Sceurman, & Jessica I. Lundin, 2012), and use of citation mapping tools in PubMed and Web of Science. Through these methods, we identified an additional 40 unique epidemiology articles (36 from the Mink et al reviews, and 4 using mapping techniques). Mink et al. included all studies in which a glyphosate risk estimate was measured, whether or not glyphosate was an *a priori* hypothesis, and regardless of the direction of the point estimate, *i.e.*, all null studies were included. In addition, HED reviewed the recently released European Food Safety Authority (EFSA) pesticide epidemiology systematic review (with searchable Excel spreadsheet) and identified an additional 5 epidemiology studies. Therefore, there were 55 studies included in this review (10 from the original search, 40 from citation mapping including evaluation of review article reference lists, and 5 from the EFSA systematic review).

Targeted searching using Google Scholar identified additional 63 unique articles using the following search string (Date searched 11/20/13):

> Google Scholar: [glyphosate epidemiology cohort OR "case control" OR "cross sectional" "human health risk"]

Because Google Scholar search tools are more limited than Medline or Web of Science, the original search could not limit to only articles of original research published in scholarly peer-reviewed journals, *i.e.*, news articles, commentary and reviews or editorials were initially identified. However, review of the 63 Google Scholar "hits" did not identify any additional original articles, not previously identified.

Upon completion of this process, we identified a total of 55 full text articles for inclusion. Attached appendices include a delineation of all references originally captured with the stated search string in both PubMed and Web of Science, and the final listing of included and excluded articles.

Appendix 4 (cont.): Included and Excluded Epidemiology Studies

	Reference:	Included? (yes/no)
1	Abass, K., Turpeinen, M., & Pelkonen, O. (2009). An evaluation of the cytochrome P450 inhibition potential of selected pesticides in human hepatic microsomes. *Journal of Environmental Science and Health Part B-Pesticides Food Contaminants and Agricultural Wastes, 44*(6), 553-563. doi: 10.1080/03601230902997766	NO
2	Acquavella, J. F., Alexander, B. H., Mandel, J. S., Burns, C. J., & Gustin, C. (2006). Exposure misclassification in studies of agricultural pesticides: insights from biomonitoring. *Epidemiology, 17*(1), 69-74.	NO
3	Acquavella, J. F., Alexander, B. H., Mandel, J. S., Gustin, C., Baker, B., Chapman, P., & Bleeke, M. (2004). Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. *Environ Health Perspect, 112*(3), 321-326.	NO
4	Acquavella, J. F., Weber, J. A., Cullen, M. R., Cruz, O. A., Martens, M. A., Holden, L. R., . . . Farmer, D. (1999). Human ocular effects from self-reported exposures to Roundup (R) herbicides. *Human & Experimental Toxicology, 18*(8), 479-486. doi: 10.1191/096032799678847087	NO
5	Acquavella, J., Farmer, D., & Cullen, M. R. (1999). A case-control study of Non-Hodgkin lymphoma and exposure to pesticides Cancer (Vol. 86, pp. 729-731). United states.	NO
6	Adomas, B., Antczak-Marecka, J., Nalecz-Jawecki, G., & Piotrowicz-Cieslak, A. I. (2013). Phytotoxicity of Enrofloxacin Soil Pollutant to Narrow-Leaved Lupin Plant. *Polish Journal of Environmental Studies, 22*(1), 71-76.	NO
7	Alavanja, M. C., Dosemeci, M., Samanic, C., Lubin, J., Lynch, C. F., Knott, C., Blair, A. (2004). Pesticides and lung cancer risk in the agricultural health study cohort. Am J Epidemiol, 160(9), 876-885. doi: 160/9/876 [pii]	YES
8	Alavanja, M. C., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C. F., . . . Blair, A. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *Am J Epidemiol, 157*(9), 800-814.	YES

9	Andreotti, G., Freeman, L. E., Hou, L., Coble, J., Rusiecki, J., Hoppin, J. A., Alavanja, M. C. (2009). Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. *Int J Cancer, 124*(10), 2495-2500. doi: 10.1002/ijc.24185	YES
10	Arbuckle, T. E., Lin, Z. Q., & Mery, L. S. (2001). An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environmental Health Perspectives, 109*(8), 851-857. doi: 10.2307/3454830	YES
11	Astiz, M., de Alaniz, M. J. T., & Marra, C. A. (2009). Effect of pesticides on cell survival in liver and brain rat tissues. *Ecotoxicology and Environmental Safety, 72*(7), 2025-2032. doi: 10.1016/j.ecoenv.2009.05.001	NO
12	Baker, B. A., Alexander, B. H., Mandel, J. S., Acquavella, J. F., Honeycutt, R., & Chapman, P. (2005). Farm Family Exposure Study: methods and recruitment practices for a biomonitoring study of pesticide exposure. *J Expo Anal Environ Epidemiol, 15*(6), 491-499. doi: 10.1038/sj.jea.7500427	NO
13	Band, P. R., Abanto, Z., Bert, J., Lang, B., Fang, R., Gallagher, R. P., & Le, N. D. (2011). Prostate Cancer Risk and Exposure to Pesticides in British Columbia Farmers. *Prostate, 71*(2), 168-183. doi: 10.1002/pros.21232	YES
14	Bolognesi, C., Carrasquilla, G., Volpi, S., Solomon, K. R., & Marshall, E. J. P. (2009). Biomonitoring of GeNOtoxic Risk in Agricultural Workers from Five Colombian Regions: Association to Occupational Exposure to Glyphosate. Journal of Toxicology and Environmental Health-Part a-Current Issues, 72(15-16), 986-997. doi: 10.1080/15287390902929741	NO
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106	Pedroso, J. A., & Silva, C. A. (2010). The nephrologist as a consultant for acute poisoning: epidemiology of severe poisonings in the State of Rio Grande do Sul and techniques to enhance renal elimination. *J Bras Nefrol, 32*(4), 340-348.	NO

107	Peterson, R. K. D., & Shama, L. M. (2005). A comparative risk assessment of genetically engineered, mutagenic, and conventional wheat production systems. *Transgenic Research, 14*(6), 859-875. doi: 10.1007/s11248-005-1411-8	NO
108	Potti, A., & Sehgal, I. (2005). Exposure to pesticides increases levels of uPA and uPAR in pre-malignant human prostate cells. *Environmental Toxicology and Pharmacology, 19*(2), 215-219. doi: 10.1016/j.etap.2004.04.010	NO
109	Ruder, A. M., Waters, M. A., Butler, M. A., Carreón, T., Calvert, G. M., Davis-King, K. E., Group, B. C. C. S. (2004). Gliomas and farm pesticide exposure in men: the upper midwest health study. *Arch Environ Health, 59*(12), 650-657.	YES
110	Rull, R. P., Ritz, B., & Shaw, G. M. (2006). Neural tube defects and maternal residential proximity to agricultural pesticide applications. *American Journal of Epidemiology, 163*(8), 743-753. doi: 10.1093/aje/kwj101	YES
111	Saldana, T. M., Basso, O., Hoppin, J. A., Baird, D. D., KNOtt, C., Blair, A., . . . Sandler, D. P. (2007). Pesticide exposure and self-reported gestational diabetes mellitus in the agricultural health study. Diabetes Care, 30(3), 529-534. doi: 10.2337/dc06-1832	YES
112	Sanin, L. H., Carrasquilla, G., Solomon, K. R., Cole, D. C., & Marshall, E. J. (2009). Regional differences in time to pregnancy among fertile women from five Colombian regions with different use of glyphosate. *J Toxicol Environ Health A, 72*(15-16), 949-960. doi: 10.1080/15287390902929691	YES
113	Sathyanarayana, S., Basso, O., Karr, C., LozaNO, P., Alavanja, M., Sandler, D., & Hoppin, J. (2010). Maternal Pesticide Use and Birth Weight in the Agricultural Health Study. Journal of Agromedicine, 15(2), 127-136. doi: 10.1080/10599241003622699	YES
114	Savitz, D. A., Arbuckle, T., Kaczor, D., & Curtis, K. M. (1997). Male pesticide exposure and pregnancy outcome. *Am J Epidemiol, 146*(12), 1025-1036.	YES
115	Schilmann, A., Lacasana, M., Blanco-MuNOz, J., Aguilar-GarduNO, C., Salinas-Rodriguez, A., Flores-Aldana, M., & Cebrian, M. E. (2010). Identifying pesticide use patterns among flower growers to assess occupational exposure to mixtures. Occup Environ Med, 67(5), 323-329. doi: 10.1136/oem.2009.047175	NO

116	Semal, J. (2007). Patentability of living organisms: From biopatent to bio-big-bang. *Cahiers Agricultures, 16*(1), 41-48.	NO
117	Senior, I. J., & Dale, P. J. (2002). Herbicide-tolerant crops in agriculture: oilseed rape as a case study. *Plant Breeding, 121*(2), 97-107. doi: 10.1046/j.1439-0523.2002.00688.x	NO
118	Settimi, L., Davanzo, F., Travaglia, A., Locatelli, C., Cilento, I., Volpe, C., Urbani, E. (2007). [Italian Program for Surveillance of Acute Pesticide-Related Illnesses: cases identified in 2005]. *G Ital Med Lav Ergon, 29*(3 Suppl), 264-266.	NO
119	Shi, G., Peng, M. C., & Jiang, T. (2011). MultiMSOAR 2.0: an accurate tool to identify ortholog groups among multiple geNOmes. PLoS One, 6(6), e20892. doi: 10.1371/journal.pone.0020892	NO
120	Slager, R. E., Poole, J. A., LeVan, T. D., Sandler, D. P., Alavanja, M. C., & Hoppin, J. A. (2009). Rhinitis associated with pesticide exposure among commercial pesticide applicators in the Agricultural Health Study. *Occup Environ Med, 66*(11), 718-724. doi: 10.1136/oem.2008.041798	YES
121	Slager, R. E., Simpson, S. L., Levan, T. D., Poole, J. A., Sandler, D. P., & Hoppin, J. A. (2010). Rhinitis associated with pesticide use among private pesticide applicators in the agricultural health study. *J Toxicol Environ Health A, 73*(20), 1382-1393. doi: 10.1080/15287394.2010.497443	YES
122	Smart, T., & Torres, G. (1996). Antiviral roundup. *GMHC Treat Issues, 10*(8), 6-7.	NO
123	Solomon, K. R., Anadon, A., Carrasquilla, G., Cerdeira, A. L., Marshall, J., & Sanin, L. H. (2007). Coca and poppy eradication in Colombia: environmental and human health assessment of aerially applied glyphosate. *Rev Environ Contam Toxicol, 190*, 43-125.	NO
124	Solomon, K. R., Marshall, E. J. P., & Carrasquilla, G. (2009). Human Health and Environmental Risks from the Use of Glyphosate Formulations to Control the Production of Coca in Colombia: Overview and Conclusions. *Journal of Toxicology and Environmental Health-Part a-Current Issues, 72*(15-16), 914-920. doi: 10.1080/15287390902929659	NO
125	Sowers, V. (1992). Healthcare uniform service market poised for expansion. *Text Rent, 75*(9), 38, 40, 42-34.	NO

126	Valcin, M., Henneberger, P. K., Kullman, G. J., Umbach, D. M., London, S. J., Alavanja, M. C. R., Hoppin, J. A. (2007). Chronic bronchitis among NOnsmoking farm women in the agricultural health study. Journal of Occupational and Environmental Medicine, 49(5), 574-583. doi: 10.1097/JOM.0b013e3180577768	YES
127	van Haver, E., Alink, G., Barlow, S., Cockburn, A., Flachowsky, G., Knudsen, I., Williams, A. (2008). Safety and nutritional assessment of GM plants and derived food and feed: The role of animal feeding trials. *Food and Chemical Toxicology, 46*, S2-S70. doi: 10.1016/j.fct.2008.02.008	NO
128	Varona, M., Lucia Henao, G., Diaz, S., Lancheros, A., Murcia, A., Rodriguez, N., & Hugo Alvarez, V. (2009). Effects of aerial applications of the herbicide,glyphosate and insecticides on human health. *Biomedica, 29*(3), 456-475.	NO
129	Wang, G., Fan, X. N., Tan, Y. Y., Cheng, Q., & Chen, S. D. (2011). Parkinsonism after chronic occupational exposure to glyphosate *Parkinsonism Relat Disord* (Vol. 17, pp. 486-487). England.	NO
130	WECHSLER, L., CHECKOWAY, H., FRANKLIN, G., & COSTA, L. (1991). A PILOT-STUDY OF OCCUPATIONAL AND ENVIRONMENTAL RISK-FACTORS FOR PARKINSONS-DISEASE. *Neurotoxicology, 12*(3), 387-392.	YES
131	Wester, R. C., Melendres, J., Serranzana, S., & Maibach, H. I. (1994). Time-response necessary in validation for extraction of pesticides from cloth patches used in field exposure studies. *Arch Environ Contam Toxicol, 27*(2), 276-280.	NO
132	Williams, A. L., Watson, R. E., & DeSesso, J. M. (2012). DEVELOPMENTAL AND REPRODUCTIVE OUTCOMES IN HUMANS AND ANIMALS AFTER GLYPHOSATE EXPOSURE: A CRITICAL ANALYSIS. *Journal of Toxicology and Environmental Health-Part B-Critical Reviews, 15*(1), 39-96. doi: 10.1080/10937404.2012.632361	NO
133	Williams, G. M., Kroes, R., & Munro, I. C. (2000). Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. *Regul Toxicol Pharmacol, 31*(2 Pt 1), 117-165. doi: 10.1006/rtph.1999.1371	NO

134	Yiin JH, Ruder AM, Stewart PA, Waters MA, Carreón T, Butler MA, Calvert GM, Davis-King KE, Schulte PA, Mandel JS, Morton RF, Reding DJ, Rosenman KD; Brain Cancer Collaborative Study Group. The Upper Midwest Health Study: a case-control study of pesticide applicators and risk of glioma. Environ Health. 2012 Jun 12;11:39.	YES
135	Zawahir, S., Roberts, D. M., Palangasinghe, C., Mohamed, F., Eddleston, M., Dawson, A. H., Gawarammana, I. (2009). Acute intentional self-poisoning with a herbicide product containing fenoxaprop-P-ethyl, ethoxysulfuron, and isoxadifen ethyl: a prospective observational study. Clin Toxicol (Phila), 47(8), 792-797. doi: 10.1080/15563650903174810	NO

To: Kent, Ray[Kent.Ray@epa.gov]
From: Miller, David
Sent: Tue 3/24/2015 5:46:42 PM
Subject: FW: German regulators responding to questions related to glyphosate/cancer
Glyphosate D417808 mem.pdf

FYI – I am sure at one point in the last year I have sent you the attached. But here it is, per discussion.

David.

From: Miller, David
Sent: Tuesday, March 24, 2015 12:39 PM
To: Jordan, William
Subject: RE: German regulators responding to questions related to glyphosate/cancer

Thanks.

Ex. 5 - Deliberative Process

David.

From: Jordan, William
Sent: Tuesday, March 24, 2015 12:25 PM
To: Miller, David
Subject: FW: German regulators responding to questions related to glyphosate/cancer

FYI

Bill

William Jordan

Deputy Director, Programs

Office of Pesticide Programs

U. S. Environmental Protection Agency

Phone: 703-305-1049

Fax: 703-308-4776

Mailing Address:
USEPA Headquarters
Clinton Building
1200 Pennsylvania Ave., NW
Mail Code (7501P)
Washington, DC 20460

Courier Address:
Potomac Yards South
2777 Crystal Drive
Room 12-235
Arlington, VA

From: Overstreet, Anne

Sent: Tuesday, March 24, 2015 10:31 AM
To: Sisco, Debby; Jordan, William; Strauss, Linda; Han, Kaythi; Dinkins, Darlene
Subject: German regulators responding to questions related to glyphosate/cancer

FYI – the information below was apparently from German regulators in response to inquiries related to glyphosate.

Anne Overstreet, Chief
Communication Services Branch
Field and External Affairs Division
Office of Pesticide Programs
Environmental Protection Agency
overstreet.anne@epa.gov
(703)308-8068

From: Goodis, Michael
Sent: Tuesday, March 24, 2015 10:26 AM
To: Overstreet, Anne
Subject: FW:

FYI to keep you in the loop

Michael L. Goodis, P.E.

Associate Director, Pesticide Re-evaluation Division (7508P)

Office of Pesticide Programs

US Environmental Protection Agency

Phone: 703-308-8157

goodis.michael@epa.gov

From: JENKINS, DANIEL J [AG/1920] [mailto:daniel.j.jenkins@monsanto.com]
Sent: Tuesday, March 24, 2015 10:24 AM
To: JENKINS, DANIEL J [AG/1920]; Goodis, Michael
Cc: Keigwin, Richard; Cyran, Carissa; Rowland, Jess; Anderson, Neil; Housenger, Jack
Subject: RE:

The German Regulators have responded. We hope that EPA would consider the following in their approach to responses:

Does Glyphosate cause cancer?

(English translation of text at http://www.bfr.bund.de/cm/343/loest-glyphosat-krebs-aus.pdf)

Communication 007/2015 BfR March 23, 2015

Glyphosate, the ingredient in plant protection products, was deemed non-carcinogenic after review by national, European and other international institutions including the Joint Meeting on Pesticide Residues of the World Health Organisation and UN Food and Agriculture Organisation, of all the studies at their disposal.

At a meeting of the International Agency for Research on Cancer (IARC) of the World Health Organization in Lyon in March 2015, experts gathered to discuss glyphosate and, based on the studies they looked at, came to a different classification, namely as a Group 2A carcinogen, or "probably" carcinogenic for humans. This Classification was published in a short report in the journal "Lancet" on March 20, 2015.

The (German) Federal Institute for Risk Assessment (BfR) was appointed EU rapporteur for glyphosate as part of the EU re-evaluation and is commenting on this IARC Classification on the basis of the summary that was published.

Seventeen experts from 11 countries met at the IARC in March 2015 to weigh the carcinogenicity or potential carcinogenicity of four organophosphates and glyphosate, none of which has been classified by the competent European authorities as carcinogenic or mutagenic.

On the basis of the information at the BfR's disposal, the classification of glyphosate in the Lancet on March 20 as belonging to Group 2A (probably carcinogenic to humans) is **scientifically hard to follow and apparently based on very few studies**. The IARC decision

cannot be judged definitively, however, since the final IARC Monograph, in which its decision will be backed up with more information, is not yet published.

The recently published IARC classification is based partially on indications of carcinogenic effect in human studies, i.e. a statistical relationship between exposure to glyphosate and an increased risk of non-Hodgkin lymphomas. This risk is derived from three epidemiological studies from the USA, Canada and Sweden. However, this conclusion was not shared a very large scale "Agricultural Health Study", also cited, or by other studies. **In the current report of the BfR to the EU, on the other hand, over 30 epidemiological studies were evaluated. In the comprehensive opinion, there was no proven relationship between exposure to glyphosate and an increased risk of non-Hodgkin's lymphoma or other types of cancer.**

Furthermore, IARC advances findings from animal testing as proof of a carcinogenic effect of glyphosate. All of these findings were also considered in the glyphosate appraisals of the BfR, the EU institutions and the Joint Meeting on Pesticide Residues of the WHO and FAO, which is responsible for the appraisal of pesticide ingredients. These organizations came to the overall conclusion that glyphosate is not carcinogenic. The BfR does not know how many of the 11 long-term studies on rats and mice considered valid by the BfR were available to the IARC.

The theory advanced in one study that skin tumors could be caused by a highly concentrated, irritant formulation with the ingredient were also not regarded by the EU institutions as proof for the carcinogenic qualities of glyphosate.

Indications for a gene toxic potential of glyphosate cannot be concluded from IARC's published summary, since the review also included formulations that were not further described.

The fact that different bodies reach different conclusions from different information and interpretations of experimental data is a daily reality in risk assessment. The BfR will examine IARC'sclassification in detail once the Monograph is published.

Dan Jenkins
U.S. Agency Lead

Regulatory Affairs
Monsanto Company
1300 I St., NW
Suite 450 East
Washington, DC 20005

Office: 202-383-2851

Cell: 571-732-6575

From: JENKINS, DANIEL J [AG/1920]
Sent: Monday, March 23, 2015 10:10 AM
To: 'goodis.michael@epa.gov'
Cc: 'Keigwin, Richard'; 'Cyran, Carissa'; 'rowland.jess@epa.gov'; 'anderson.neil@epa.gov'
Subject:

Mike:

Per our phone conversation. We hope EPA will correct mistakes or absences of fact with respect to its record on glyphosate (including the 2013 statement and the AHS study) as it relates to carcinogenicity.

2009 EPA Glyphosate Reg Review

Carcinogenicity was not identified as a concern in the work plan
http://www.epa.gov/oppsrrd1/registration_review/glyphosate/

2013 Federal Register Notice (FR 25396 Vol. 78, No. 84, Wednesday, May 1, 2013) Final Rule new tolerances in or on multiple commodities: "EPA has concluded that glyphosate does not pose a cancer risk to humans."

http://www.gpo.gov/fdsys/pkg/FR-2013-05-01/pdf/2013-10316.pdf

"For the herbicide **glyphosate**, there was *limited evidence of carcinogenicity* in humans for non-Hodgkin lymphoma. The evidence in humans is from studies of exposures, mostly agricultural, in the USA, Canada, and Sweden published since 2001. In addition, there is convincing evidence that glyphosate also can cause cancer in laboratory animals. On the basis of tumours in mice, the

United States Environmental Protection Agency (US EPA) originally classified glyphosate as *possibly carcinogenic to humans* (Group C) in 1985. After a re-evaluation of that mouse study, the US EPA changed its classification to *evidence of non-carcinogenicity in humans* (Group E) in 1991. The US EPA Scientific Advisory Panel noted that the re-evaluated glyphosate results were still significant using two statistical tests recommended in the IARC Preamble. The IARC Working Group that conducted the evaluation considered the significant findings from the US EPA report and several more recent positive results in concluding that there is *sufficient evidence of carcinogenicity* in experimental animals. Glyphosate also caused DNA and chromosomal damage in human cells, although it gave negative results in tests using bacteria. One study in community residents reported increases in blood markers of chromosomal damage (micronuclei) after glyphosate formulations were sprayed nearby."

http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)70134-8/abstract

http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

Thanks,

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U.S. Agency Lead

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: February 6, 2014

SUBJECT: Glyphosate: Tier II Incident Report

PC Code: 103601, 103603, 103604, 103605, 103607, 103608, 103613, 417300
Decision No.: 487242
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA

MRID No.: NA

DP Barcode: D417808

Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 38641-94-0, 70393-85-0, 40465-66-5, 114370-14-8, 70901-12-1, 1071-83-6
40 CFR: NA

Ver.Apr.08

FROM: Shanna Recore, Industrial Hygienist
Carol Christensen, Epidemiologist
Elizabeth Evans, Environmental Protection Specialist
Khin Oo, MD, DABT, Environmental Health Scientist
Toxicology and Epidemiology Branch
Health Effect Division (7509P)

THROUGH: David J. Miller, Acting Chief
Toxicology and Epidemiology Branch
Health Effects Division (7509P)

06-FEB-2014

TO: Thomas Bloem, Risk Assessor
Risk Assessment Branch I
Health Effects Division (7509P)

SUMMARY

HED is currently re-evaluating the toxicity, exposure, and risk profile of glyphosate under the Food Quality Protection Act (FQPA)-mandated Registration Review program. The registration review program is designed to ensure EPA evaluates new information regarding pesticides on a 15 year cycle, and to update the risk assessment and initiate new regulatory requirements, when appropriate, to ensure the protection of human health and the environment. Pesticides included in

the registration review program are pesticides for which EPA completed a Re-registration Eligibility Decision (RED) under the FQPA.

One component of the Agency's Registration Review Program is consideration of acute and chronic health effects observed in the human population as a possible consequence of glyphosate exposure. Given the magnitude and frequency observed in the initial screening evaluation of acute poisoning incidents related to glyphosate use, HED determined that a more extensive Tier II report of the acute and chronic human health effects linked to glyphosate use should be performed. A Tier II report provides additional details and greater depth in scope of review information relating to human exposure. Information streams queried for this report include acute pesticide poisoning event (incident data) and surveillance data, medical case reports of human exposure to glyphosate, general medical information, biomonitoring data, and observational epidemiology studies. Utilization of these data will aid HED in better defining and characterizing the potential risk of glyphosate pesticide products to the U.S. population, and particular sub-groups such as workers and children.

A review of medical literature finds most of the accidental ingestions of glyphosate formulations resulted in mild symptoms such as irritation of oral and upper gastrointestinal mucosa and were self limited. However, intentional ingestions caused moderate to severe symptoms in multiple organs.

HED reviewed five pesticide incident data sources (IDS, NPIC, California PISP, NIOSH/SENSOR, and AAPCC). HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report, and the other databases and medical literature reviewed. These health effects primarily include dermal, ocular, and respiratory. HED did not identify any aberrant effects outside of those anticipated. While inconvenient for those who suffer adverse health effects, effects are generally mild/minor to moderate and resolve rapidly. The incident data available from IDS and NPIC suggest that homeowner mixing/loading/ applying (usually due to human errors and container leaks of glyphosate products) are responsible for almost half of the reported incidents. SENSOR-Pesticides incident data are consistent with IDS and NPIC, also suggesting that most reported incidents (50%) occur during application of glyphosate results. . However, the SENSOR-Pesticide incidents include both residential and occupational incidents. The incident data available from CA PISP suggests that occupational handling of equipment is responsible for most incidents due to equipment leaks and malfunction.

All of the databases showed a number of childrens' exposures (ranging from 5% to 27% of total cases). Based on the data in SENSOR, IDS, and NPIC, it appears that the childrens' exposures are due to primarily to postapplication exposure, accidental ingestion, and tampering with the product.

Ocular exposure and symptoms were reported in all of the databases, to both occupational and nonoccupational users, as a result of splash to the face or touching their eyes with the product on their hands. These symptoms primarily included eye irritation, redness, burning and blurred vision.

Trends over time data from IDS (2008 to 2012), PISP (2005 to 2010), SENSOR-Pesticides (1998 to 2009) and AAPCC (2001 to 2012) data were reviewed. Based on IDS and AAPCC, which are primarily non-occupational cases, incidents appear to be decreasing over time. CA PISP data represents both occupational and non-occupational incidents. This data appears to show incidents to be relatively steady over time. The SENSOR-Pesticide data also represent both occupational and non-occupational cases. For this data, occupational case reports involving glyphosate appeared to be increasing until 2008 and non-occupational case reports appear to be increasing over time. The increase in non-occupational case reports may be reflective of increased SENSOR state capacity to collect non-occupational pesticide surveillance data.

While HED identified several dozen glyphosate environmental epidemiology studies, few of these studies reflected an *a priori* research interest in the potential role of glyphosate and chronic disease outcomes, and most studies were hypothesis-generating in nature. Given this and other limitations of these studies, we cannot conclude glyphosate plays a role in any of the health outcomes studied across this epidemiologic database. EPA will continue to follow the literature concerning the potential role of the chemical in certain cancer and non-cancer outcomes, particularly respiratory health and lymphohematopoietic cancers such as non-Hodgkin lymphoma (NHL) and multiple myeloma (MM).

1. BACKGROUND

Glyphosate is a nonselective herbicide which acts via blocking the activity of the enzyme, 5-enolpyruvylshikimate 3-phosphate synthase (EPSPS). EPSPS is produced only by green plants and is involved in the synthesis of the amino acids tyrosine, tryptophan, and phenylalanine.

Glyphosate is registered for use on a variety of fruit, vegetable, and field crops as well as for aquatic and terrestrial uses. It is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Glyphosate was first registered for use by the United States Environmental Protection Agency (U.S. EPA) in 1974 and reregistration was completed in 1993. Glyphosate is among the most widely used pesticides by volume. It ranked eleventh among conventional pesticides used in the U.S. during 1990-91. In recent years, approximately 13 to 20 million acres were treated with 18.7 million pounds of glyphosate annually. The largest use sites include hay/pasture, soybeans and field corn (D362745, 06/03/2009, J. Langsdale et al.).

In March 2009, HED prepared a preliminary Tier I human incident review of glyphosate human incident reports by consulting the OPP Incident Data System (IDS) for reports of poisoning incidents. During the time period captured in the screening report, 2002 to March 2009, 289 incidents involved products containing the single active ingredient glyphosate. Based on the IDS, 8 major types of adverse health effects were identified: gastro-intestinal (4.8%), dermal (30.1%), upper-respiratory (10.3%), neurological (34.3%), cardiovascular (0.3%), ocular (13.8%), muscular (0.3%), and combination (5.5%) effects (*Updated Review of Glyphosate Incident Reports*, M. Hawkins and J. Cordova, 03/12/2009). Given the frequency and relative severity, HED determined it would further evaluate glyphosate acute poisoning event reporting and surveillance databases as well as a review of published literature as to the acute and chronic health effects associated with glyphosate exposure by performing a Tier II review.

It is important to recognize, however, that reports of adverse health effects allegedly due to a specific pesticide exposure (i.e., an "incident") are largely self-reported and therefore, generally speaking, neither exposure to a pesticide or reported symptoms (or the connection between the two) are validated. Therefore, only rarely can causation be determined or definitively identified based on incident data. However, incident information can provide important feedback to the Agency. Human incident data, in concert with other human observational studies (medical case reports, general medical information, biomonitoring and epidemiological studies) and the human health risk assessment, can assist the Agency in determining potential risks of pesticides/pesticide product exposure, and can help characterize that risk. This review assesses acute pesticide poisoning incidents, medical case reports, and published epidemiology studies to inform the preliminary risk assessment for glyphosate.

a. Tier II Overview

Historically, the Agency has relied on toxicity studies conducted on animals and exposure information measured or modeled in relevant populations regarding the pesticide's use pattern when considering the registration or re-registration of a pesticide. While the use of these data, models and standard exposure assumptions will likely not diminish, the relevance of human data that report acute and chronic health effects experienced in the population will continue to increase. Improved exposure assessment methods, use of biomarkers of disease as well as exposure, and continued merging of toxicology and epidemiology through adverse outcome pathway/MOA framework analysis and molecular epidemiology methods will enhance the utility of public health data as a stream of evidence in the risk assessment.

Tier I incident reports make recommendations on whether there is a need for a more in-depth Tier II analyses based on high frequency and/or severity of incidents in IDS, SENSOR-Pesticides, and the preliminary Agricultural Health Study results for a particular active ingredient. If a recommendation for further in-depth analyses (Tier II) is made, a broader set of available incident data sets are reviewed and a review of available epidemiological studies and

human toxicology and medical case reports is conducted. Trend analyses and summaries (root cause analysis) with respect to incidents is done, as well as additional analysis on a product-specific (as opposed to active ingredient) basis.

This Tier II glyphosate analysis includes human observation data from a variety of sources including:

- Human toxicological reviews and medical case reports from the literature,
- Human incident (poisoning) data from such sources as OPP's Incident Data System (IDS) database, NIOSH SENSOR, the Agency-sponsored National Pesticide Information Center (NPIC), California's Pesticide Incident Surveillance Program (PISP), American Association of Poison Control Centers (AAPCC) Annual Reports, and
- Epidemiological studies from the literature.

2. MEDICAL CASE REPORTS

a. Literature Search Methodology

While much animal toxicology data exist and have been evaluated by OPP during the glyphosate registration review process medical data involving pesticides provide another source of information to evaluate risks of glyphosate. Medical case reports evaluate particular patients and describe the symptoms, signs, diagnosis, treatment, and follow-ups. Medical case series are similar to case reports, but focus instead on multiple patients with similar exposure, treatment and/or symptoms/signs. Case reports and case series provide insight into the potential effects of pesticide exposure on humans. It is important to remember, however, that often the exposure scenarios associated with case reports and series are high dose (suicides, attempted suicides, or non-accidental ingestions) and are dissimilar in some ways to inadvertent exposures which tends to be at substantially lower doses and with different exposure routes. Nevertheless, examining these cases can be valuable in that they illustrate the effects of frankly toxic doses and allow observation of what may be important health consequences of high-dose exposure. Medical information on pesticides are found in many locations; however the Agency has relied on information from databases for the period from 1975 to the present, querying the National Library of Medicine (PubMed, TOXNET), Web of Knowledge, Google Scholar, as well as the CDC and ATSDR databases, to identify relevant pesticide medical information. Specifically, the Agency looked across the following databases for this assessment:

- PUB MED comprises more than 22 million citations for biomedical literature from MEDLINE, life science journals and online books.
- TOXNET consists of HSDB (Hazardous Substances Data Bank) which contains comprehensive peer-reviewed toxicology data for about 5,000 chemicals.

- ATSDR Case-Studies provide information regarding clinical findings, treatment and current knowledge regarding pesticides.

- Google Scholar is a search engine that indexes the full text of scholarly literature across an array of publishing formats and disciplines. It includes most peer-reviewed online journals of Europe and America's largest scholarly publishers.

The Agency is confident that considering the above sources captures the critical medical information concerning the human health effects of glyphosate. A medical literature search on glyphosate in Pub Med, Web of Knowledge and Google was performed, using the terms (or key concepts): *glyphosate toxicity*; *glyphosate, poisoning*; *glyphosate*, *symptoms*. One hundred and ninety nine citations were recovered but many of them were not related to the human health effects of glyphosate. From the title and abstract review, animal studies with glyphosate and studies regarding environmental effects of glyphosate were removed. A Google Advanced Search and the EPA library were used to retrieve full text articles. Thirty eight full text articles related to glyphosate and human health effects, toxicokinetics, toxicodynamics and case reports were reviewed.

b. Summary of glyphosate medical literature review.

Glyphosate [N-(phosphonomethyl)glycine] is a nonselective herbicide. Glyphosate inhibits the enzyme 5-enolpyruvyl-shikimic-3-phosphate-synthase in plants; however, mammals do not have this enzyme (Aaron, 2006). Glyphosate should thus possess low risk for mammalian toxicity. Glyphosate has been placed in Toxicity Category III for oral and dermal acute toxicity (i.e. oral LD_{50} 500 – 5,000 mg/kg), which means low acute toxicity for oral, and dermal exposures. It is a mild eye irritant and is not a dermal sensitizer. In addition, neurotoxicity was not observed in any of the acute, subchronic, chronic, developmental or reproductive animal studies performed with glyphosate (D398547, 11/14/2012, T. Bloem et al.).

However, glyphosate end products (commercial products) are usually formulated with different glyphosate salts with various concentrations of surfactant polyoxyethyleneamine (POEA) up to 50% and other ingredients (antifoaming agents, biocides and inorganic ions), rather than active ingredient glyphosate alone. For example, Roundup contains 41% glyphosate as the isopropylamine salt and 15% POEA. This can potentially make the end product more toxic than the active ingredient alone.

There have been many reports in the medical literature on acute poisoning with commercial glyphosate –based formulations. Most of the accidental ingestions of glyphosate formulations resulted in mild symptoms such as irritation of oral and upper gastrointestinal mucosa and were self limited. However, intentional ingestions caused moderate to severe symptoms in multiple organs. It was reported that most of these symptoms may actually be related to the surfactant polyoxyethyleneamine (POEA) or other ingredients in the commercial glyphosate formulations

(Bradberry, Proudfoot, & Vale, 2004; Sawada, Nagai, Ueyama, & Yamamoto, 1988). Since human poisoning with this herbicide is not with the active ingredient (glyphosate) alone but with various mixtures, it is not easy to identify the exact cause. Table A in Appendix 1 identifies various glyphosate product formulations that have been previously identified by the U.S. Forest Service (Diamond & Durkin, 2011).

Experimental studies have found that the toxicity of a surfactant (POEA) is greater than the toxicity of glyphosate alone (Bradberry et al., 2004; Peixoto, 2005). Hour B.T. et al. (2012) also reported that surfactants interfere with the proton gradient in the mitochondria wall, affecting energy production in cells leading to cell death. According to Peixoto F. (2005), Roundup interferes with electron transfer by partially inhibiting mitochondrial complexes II and III, leading to depressed ATPase activity. When the authors used the glyphosate alone in the same concentration they did not find this effect. Diamond (2011) mentioned that there were various concentrations of POEA surfactant, glyphosate salts and other ingredients in different glyphosate products and the resulting adverse health effects may be different. The adverse health effects of accidental and intentional exposures to glyphosate products are summarized from medical case reports in the following sections.

c. Summary of Case Reports

Various case reports are summarized in this section, and are divided into accidental/unintentional exposures and intentional exposures.

i. Accidental/Unintentional Exposures

Inhalation Exposure:

- Ptok M., (2009) reported that a 26-year-old school teacher suffered from a severe dysphonia (abnormal vocal sounds) a few hours after applying glyphosate product (more detailed information regarding the exposure was not available). She informed that she had followed the instructions on the product label. A laryngoscopy found decreased vocal fold mobility. The symptoms disappeared spontaneously and her vocal fold mobility returned to normal after 6 weeks (Ptok, 2009).
- A 42 year old worker exposed to Roundup suffered from burns in the mucosal lining of the pharynx and larynx and acute toxic pneumonitis (inflammation of lung tissue) (Pushnoy, Avnon, & Carel, 1998). He presented at the ER with shortness of breath, irritative cough, dizziness, discomfort in the throat and episodes of hemoptysis (blood in the sputum). According to the patient he developed these symptoms after cleaning the clogged sprayer containing Roundup inside a small room. His chest X-ray (Figure 1) showed extensive bilateral alveolar involvement. The authors stated that the surfactant

polyoxyethylene amine is the main reason for erosion of upper respiratory tract mucosal lining and lung tissue.

Figure 1. Chest radiograph

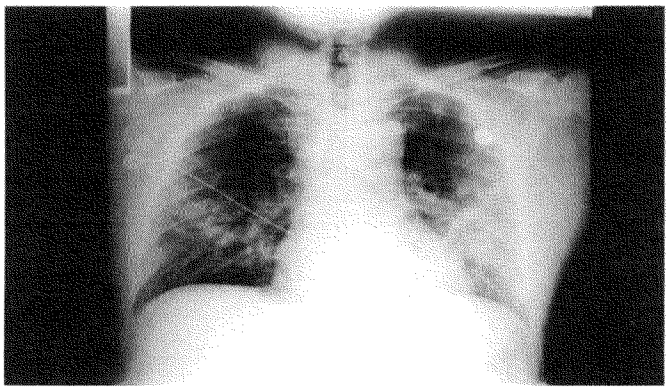


FIGURE 1. Chest radiograph on admission demonstrating interstitial bilateral infiltrations.

Dermal Exposure:

Although glyphosate alone has been found to have low dermal toxicity, there were several cases of severe dermal effects due to accidental exposure to formulations containing glyphosate and surfactants.

- Amerio et al. (2004) reported that a 78 year old woman presented with extensive chemical burns on her back, knees and legs caused by an accidental contact with a glyphosate-surfactant formulation (41% glyphosate and 15% POEA). She knelt on the ground where her son had just sprayed the herbicide. Later she put on clothing that had been lying on the same ground contaminated with the herbicide. At home, she lay down in the same clothing on the couch. After several hours she noticed burning sensation on areas that had been in touch with the glyphosate product; and sheets of necrotic epidermis (dead skin) had sloughed, causing extensive erosions. Fluid filled lesions (bullae) were also appeared on the dorsum of the feet. She was treated with normal saline wet dressing, petrolatum gauze, topical hydrocortisone 1% plus silver-sulfadiazine cream, and systemic antibiotic piperacilline/tazobactam (to prevent secondary infection). It took four weeks to heal these skin lesions. The authors mentioned that effects of glyphosate on human skin depend on several factors, such as concentration of glyphosate in the formulation, the duration of exposure, the presence of a surfactant in the formulation, and skin conditions such as moisture, sweat, and the presence of sebum (Amerio et al., 2004).

- Mariager et al. (2013) also described a 43-year old man with severe chemical burns following prolonged accidental exposure to the herbicide Roundup Bio (isopropylamine salt of glyphosate and surfactant POEA with the pH of 4.5-5). The contents accidentally

sprayed on the patient when he shook the bottle. He did not wash the exposed areas for more than 24 hours. The next day he developed local swelling, bullae and exuding wounds on his left hand, arm, upper arm and axilla regions. Soon it changed into second degree skin necrosis with detachment of the epidermis. In addition, he had touched his face with contaminated hands resulting in swelling of the area around the eye. After three months, nerve conduction studies showed reduced nerve conduction in distal axons on the medial, ulnar and radial nerves in the exposed hand. Hand X-ray done after 4 months revealed osteopenia of carpal bones. After 9 months, the patient regained near normal sensation but he had severe atrophy of the intrinsic muscles of the hand and loss of strength with decreased range of motion. All other skin lesions had healed with scarring and alopecia (hair loss), (Figures 2, 3 and 4) (Mariager, Madsen, Ebbehoj, Schmidt, & Juhl, 2013).

Figure 2: Atrophy of hand muscles resulting in deformity (Mariager TP., et al.)

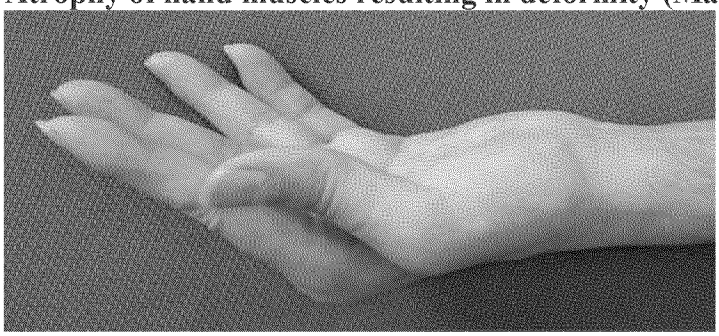


Figure 3: Osteopenia of the carpal bones (Mariager TP., et al.)

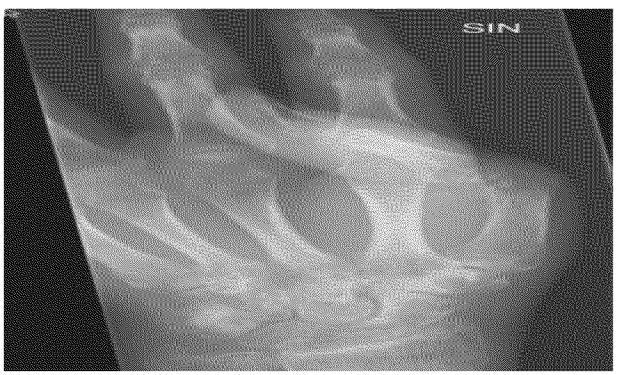
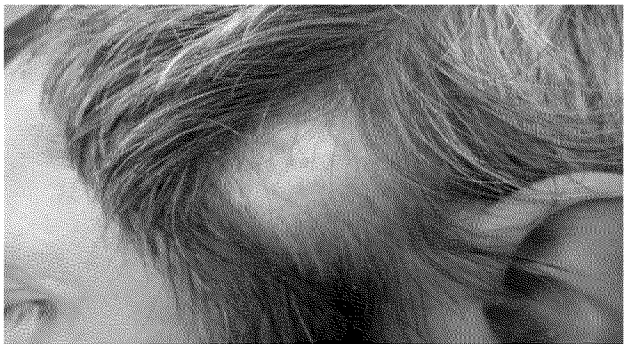
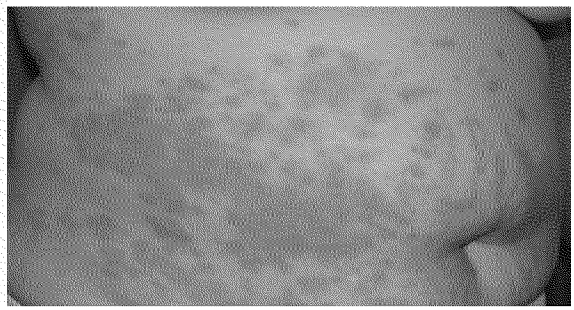


Figure 4: Chemical burn healing with alopecia (Mariager TP., et al.)



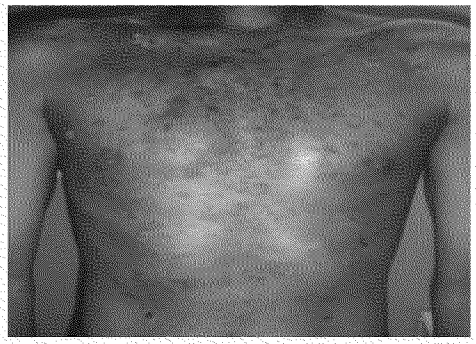
- Another dermal exposure involved a 37 year old female. She was exposed to glyphosate herbicide (Touchdown Premium) when the backpack containing the herbicide broke and wet her clothing. The herbicide contained 36% glyphosate ammonium salt which she diluted with water before using it. She admitted delaying in rinsing off the herbicide. At the end of the day she suffered from the irritant contact dermatitis, followed by erythemato-purpuric plaques developed on the upper extremities, on the abdomen, axilla and groin (Figure 5). The patient was treated with oral corticosteroids and antihistamines. The lesions got better in 2 weeks with post-inflammatory hyperpigmentation (Heras-Mendaza, Casado-Farinas, Paredes-Gascon, & Conde-Salazar, 2008).

Figure 5: Erythematous and purpuric plaques on the abdomen (Heras-Mendaza F., et al. 2008)



- Fisher KR., et al (2008) reported a patient who developed pemphigus vulgaris (PV) on his body and extremities, after an occupational exposure to fumes of burning empty glyphosate drums. PV is an autoimmune skin lesions characterized by bullae that rupture quickly and progress to crusted erosions. Authors mentioned that their patient had been using glyphosate product with 41% glyphosate isopropylamine salt on the farm for the past 3 years, which might have sensitized the skin (Figure 6) (Fisher et al., 2008).

Figure 6: Scattered bullae and vesicles on the body (Fisher KR., et al., 2008)



Accidental death with glyphosate trimesium formulation (Touchdown):

- Sorensen et al. (1999) reported an accidental ingestion of Touchdown causing the death of a 6-year-old boy. He accidentally ingested a mouthful of the herbicide and died within a couple of hours. His father had placed the bottle containing the herbicide on the table in the garage and the child mistook it for a drink. The child spat almost all of it out and swallowed only a small amount because of the bad taste. He then went into the house and drank some water. Soon he developed pain, vomiting, and then collapsed. The father performed cardiopulmonary resuscitation (CPR) when he noticed that his son was not breathing and had no pulse. The child was taken to the hospital and, in spite of the resuscitation attempt, he passed away. The post-mortem examination revealed edema of the mucus membranes of the airways, erosion of the mucus membranes of the gastrointestinal tract, pulmonary edema, cerebral edema, and dilated right atrium and ventricle of the heart (Sorensen & Gregersen, 1999).

ii. Intentional Exposures

Intentional exposure or suicide cases can assist in understanding the relative sensitivity of humans to the toxicity of glyphosate formulations. Some of the case reports may be used for estimating the acute lethal toxicity of glyphosate-surfactant formulations.

- Bradberry et al. (2004) reported that ingestion of >85 mL of the concentrated formulation can cause serious toxicity in adults. Pain in mouth, throat, stomach and dysphagia (difficulty in swallowing) due to gastrointestinal corrosion are common. In severe cases, pulmonary edema (fluid inside the lung), respiratory distress, cardiac arrhythmias (abnormal heart rhythm), shock, and impaired consciousness may occur. In addition, renal failure, metabolic acidosis and hyperkalemia (high serum potassium level) may take place requiring hemodialysis for treatment (Bradberry et al., 2004).

- Zouaoui et al. (2013) reviewed 13 cases of glyphosate herbicide intentional poisoning, and found that the most common symptoms were oropharyngeal ulcerations, nausea and vomiting. The main biochemical abnormality was lactic acidosis. Other adverse health effects were: respiratory distress; cardiac arrhythmia; hyperkalemia; impaired renal function; liver toxicity; and altered consciousness. In mild to moderate intoxications, blood glyphosate concentrations were in the range of (0.6 – 150) mg/L with a mean value of 61 mg/L. In the severe intoxication case, the blood glyphosate concentration was found at 838 mg/L; and in fatal cases the range of (690-7480) mg/L with a mean value of 4146 mg/L was found (Zouaoui, Dulaurent, Gaulier, Moesch, & Lachatre, 2013).

- Chang CY., et al., (1999) studied lesions in gastrointestinal tract of 50 patients with glyphosate-surfactant oral ingestion as a suicide attempt. They found that esophageal injury was seen in 68% of the patients (15% grade 1, 15% grade 2a and 4% grade 2b); gastric injury in 72% (22% grade 1 and 8% grade 2a), and duodenal injury in 16% (7% grade 1 and 1% grade 2a). [According to the Zargar's modified grading system, Grade 1 injuries have swelling and redness of mucosa. Grade 2a injuries have friability, hemorrhage, erosion, blistering, whitish membranes, exudates or superficial ulcerations. Grade 2b injuries have features of grade 2a plus circumferential ulcerations] (C. Y. Chang et al., 1999). Chen HH., et al., (2013) stated that patients with grade 2b esophageal injury suffered from a greater incidence of respiratory (100.0% versus 5.9%, $P = 0.001$) and gastrointestinal (66.7% versus 11.8%, $P = 0.034$) complications than patients with grade 1 injury (H. H. Chen et al., 2013).

- Talbot and Shiaw (1991) reviewed 93 cases of exposure to Roundup from 1980 to 1989. They found that the lethal cases had ingested glyphosate herbicide (41% solution), ranging from 85-200 mL. These patients had: erosion of gastrointestinal tract (66%); sore throat (43%); dysphagia (31%): and gastrointestinal hemorrhage (8%). Other organs involved were: non-specific leucocytosis in blood (65%); pulmonary edema (23%); liver dysfunction (19%); cardiovascular shock (18%); kidney dysfunction (14%); and central nervous system (changes in the level of consciousness) (12%) (Talbot et al., 1991).

- A case-control study conducted by Lee C.H. et al., (2008) and a retrospective study done by Lee H.L. et al., (2000) found similar multi-organ effects. Author's found that useful indicators for predicting serious outcome from commercial glyphosate product were: metabolic acidosis; hyperkalemia; respiratory distress requiring intubation; tachycardia; and elevated serum creatinine levels. According to authors, pulmonary toxicity and renal toxicity were mostly responsible for the fatality (C. H. Lee, Shih, Hsu, Hung, & Lin, 2008; H. L. Lee, Chen, Chi, Huang, & Tsai, 2000).

- Kamijo Y. et al. (2012) and Bando H. et al. (2010) reported that ingestion of Roundup Maxload (48% glyphosate potassium salt) can cause severe hyperkalemia and severe complications (Bando et al., 2010; Kamijo, Mekari, Yoshimura, Kan'o, & Soma, 2012). A 69- year old female had serum potassium levels of 10.7 mEq/L (normal range is 3.5 – 5 mEq/L), loss of consciousness, low blood pressure, metabolic acidosis and abnormal cardiac rhythm (ventricular tachycardia) after ingesting about 500 mL of Roundup Maxload. Serum glyphosate levels on admission and after 20 hours were 1625.74 and 100.44 µg/mL, respectively. Chest X-rays showed diffuse pulmonary infiltrate. The endoscopy showed pharyngeal edema, esophageal erosions, and gastric erosions. Patient was given activated charcoal and put on cardiopulmonary support, continuous hemodialysis, and mechanical ventilation. Although the patient recovered, the authors reminded that glyphosate products containing high potassium that can be easily purchased in retail stores possess a serious problem in Japan.

- Stella J. and Ryan M. (2004) stated that the triad of pulmonary edema, metabolic acidosis, and hyperkalemia indicates a poor outcome, and may not respond to even the most intensive supportive care (Stella & Ryan, 2004).

- Chang CB., et al. (2009) also reported that a 57-year old woman who ingested 400 ml of a Taiwanese glyphosate formulation (41% glyphosate isopropylamine and 15% polyoxyethyleneamine) died in spite of intensive treatment. On admission to the hospital, the patient was drowsy although vital signs were within the normal range. Shock and respiratory failure developed within 5 hours after admission to the hospital. She was transferred to the intensive care unit, put on the mechanical ventilator, and treated according to the critical care procedures. The hyperkalemia was corrected with insulin/glucose infusion and oral kayexalate. The acidosis was corrected by intermittent sodium bicarbonate infusions. However, refractory shock persisted despite the administration of fluids, dopamine, vasopressin, epinephrine, and norepinephrine. Ventricular tachycardia developed on the third day of admission and the patient died (C. B. Chang & Chang, 2009).

- Although animal studies found that absorption of glyphosate from the stomach is inefficient, Roberts DM., et al. (2010) stated that in humans, commercial glyphosate solution is rapidly absorbed from the GI tract, and followed first-order elimination with a half-life ranged from (2.7-3.6) hours. This reflects the rapid development of adverse health effects in humans (Roberts et al., 2010).

- Sribanditmongkol P., et al. (2012) reviewed the pathological and toxicological results of a fatal poisoning case. The postmortem examination of a 37-year old woman who ingested 500 mL of concentrated Roundup formulation (41% glyphosate as the

isopropylamine salt and 15% polyoxyethylene amine) revealed hemorrhagic areas in the gastric mucosa and marked dilatation and thin walls in the small intestines. A mild degree of pulmonary congestion and edema was observed in both lungs. The glyphosate level in the serum was 3.05 mg/mL; the glyphosate level in the gastric contents was 59.72 mg/mL (Sribanditmongkol, Jutavijittum, Pongraveevongsa, Wunnapuk, & Durongkadech, 2012).

- According to Wu J.Y. (2006), intravenous injection of 250 mL of diluted glyphosate (150 mL of glyphosate in 500 mL of water) in a suicide attempt caused acute hemolysis (rupturing red blood cells inside the blood vessels) in a 22-year-old male patient (Wu, Chang, Tseng, Deng, & Lee, 2006).

iii. Direct Renal Toxicity

- Yoo et al. (2009) found that the product (41% glyphosate with surfactant) can cause direct toxic effects on kidneys. Their patient had suffered from the severe tubulointerstitial nephritis without the cardiovascular collapse which means that the renal insufficiency in this case was not secondary to the low blood pressure and poor renal perfusion, but due to direct toxic effect of glyphosate product on kidneys. He was admitted to the hospital 30 minutes after ingesting 90 mL of glyphosate herbicide. On arrival, his serum creatinine was normal (0.8 mg/dL) and other laboratory findings including liver, cardiac, and muscle enzymes were within normal ranges. Two days after admission, although his vital signs were stable, his serum creatinine abruptly increased to 8.2 mg/dL and oliguria (very low urine output due to renal insufficiency) developed. The kidney biopsy also showed the chemical/glyphosate-induced nephrotoxic injury. He was treated with hemodialysis and two weeks later, his renal function started to improve slowly (Yoo & BS., 2010).

iv. Neurotoxicity

Although neurotoxicity was not observed in any of the acute, subchronic, chronic, developmental or reproductive animal studies performed with the glyphosate, there were few case reports with central nervous system effects suggesting direct neuronal toxic effects from the glyphosate-surfactant herbicide (GlySH).

- Malhotra et al. (2010) reported that a 71-year-old male who attempted suicide with the commercial glyphosate formulation developed a prolonged (>7days) but reversible encephalopathy. He also had cardiogenic shock and severe metabolic acidosis (pH 7.13; HCO_3 13.2 mmol/L). His blood acetylcholinesterase level was within normal range. Authors mentioned that although glyphosate has a carbon and phosphorus moiety it does not inhibit acetylcholinesterase enzyme unlike organophosphate pesticides. The EEG (electroencephalogram) indicated encephalopathy. He was treated in the intensive care

unit and also received hemodialysis. He fully recovered after 15 days in the hospital (Malhotra, Ghia, Cordato, & Beran, 2010).

- A case of aseptic meningitis after ingestion of about 150 mL of commercial glyphosate herbicide (41% glyphosate and 15% polyoxyethyleneamine) was reported by Sato C et al. (2011). A 58 year-old female presented with signs and symptoms of meningitis such as neck stiffness, rigidity of limbs, Kernig's sign (severe stiffness of the hamstring muscle causing an inability to straighten the leg when the hip is flexed to 90 degrees), and altered consciousness. All bacteriological and virological tests were negative. Glyphosate level in the cerebrospinal fluid (CSF) was 122.5 μg/ml. Authors mentioned that signs and symptoms of meningitis decreased as the concentration of glyphosate in CSF decreased. She completely recovered after 39 days due to the aggressive supportive care in the intensive care unit. The authors determined that the findings were suggestive of aseptic meningitis caused by the commercial glyphosate poisoning (Sato, Kamijo, Yoshimura, & Ide, 2011).

- Potrebic et al. (2009) described the neurologic lesion of a 56-year old woman who ingested about 500 mL of herbicide containing glyphosate isopropylamine salt. She suffered from hypotension, hyperkalemia, respiratory and renal failure and fell into a coma. Although the patient received the intensive care, she did not regain consciousness. An MRI revealed bilateral extensive white matter lesions of the brain stem and Pons (Potrebic, Jovic-Stosic, Vucinic, Tadic, & Radulac, 2009).

- Wang G., et al (2011) reported that a previously healthy 44 year-old woman presented with rigidity, slowness and resting tremor (typical of Parkinsonism) in all four limbs. She had worked exclusively at the glyphosate production division for 3 years while wearing only basic personal protective equipment (PPE) (gloves or face mask) for 50 hours a week. The MRI revealed bilateral hypotense lesions in the globus pallidus, the substantia nigra, and in the cerebral peduncle of the brain. Authors stated that the patient's occupational history and MRI results indicated a secondary Parkinsonism due to glyphosate product, rather that primary idiopathic Parkinson's disease (G. Wang, Fan, Tan, Cheng, & Chen, 2011).

v. Determination of blood glyphosate level and urine level of metabolite

Serum glyphosate and its metabolite aminomethyl phosphonic acid (AMPA) in urine can be determined by gas chromatography-mass spectrometry (GC-MS) (Hori, Fujisawa, Shimada, & Hirose, 2003; Motojyuku et al., 2008). Wang Y., et al., 2012 reported that ion chromatography is a simple, sensitive and accurate method to prove that the patient had a glyphosate poisoning (Y. Wang, Wu, Lian, & Shi, 2012).

d. Conclusion

Although animal studies showed glyphosate to have limited toxicity, medical case reports suggest that glyphosate end use products (formulated with, different types of glyphosate salts and various concentrations of surfactants and adjuvants), may be more toxic than the active ingredient alone. Since human poisoning reviewed were not with the active ingredient (glyphosate) alone but with various mixtures, it is not easy to identify the exact cause. Nevertheless, the medical literature reviewed indicates that most of the accidental ingestions of glyphosate formulations resulted in mild symptoms such as irritation of oral and upper gastrointestinal mucosa and were self limited. However, intentional ingestions caused moderate to severe symptoms in multiple organs.

3. HUMAN INCIDENT DATA

As indicated above, incident information can provide important feedback to the Agency, assisting in determining actual real-world exposures and risks posed by pesticides/pesticide products. Incident data are collected systematically, but differently, across the different databases used by the Agency with respect to such issues as coverage, certainty/confidence, fields/parameters reported, and usability. The aforementioned five pesticide incident data sources (IDS, NPIC, AAPCC, California PISP, and NIOSH/SENSOR) were used in this glyphosate report since they provide useful content and historical perspective. Various other comparable sources of data are available (e.g. the Bureau of Labor Statistics, emergency room outpatient surveillance, National Poison Data System (NPDS), etc.) but are not included in this review. By looking across the five data sources which were used, the Agency is confident that we are considering adequate and appropriate information to discern trends and patterns in glyphosate-associated acute pesticide poisonings, or "incidents."

a. OPP Incident Data System (IDS) (2008-2013)

The OPP IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6 (a) (2) reports from registrants and reports from other federal and state health and environmental agencies and individual consumers. Since 1992, OPP has compiled these reports in IDS. IDS contain reports from across the U.S. and most incidents contained in the system have all relevant product information recorded. Case reports or "narratives" are provided for each incident, with varying levels of detail; however, there is no effort at validating or assessing how likely it is that the reported exposure is causally related to the reported outcome. Because IDS has such extensive coverage, it is useful for providing temporal trend and geographic pattern information. The system is also useful for determining whether risk mitigation has helped reduce potential pesticide exposure through a decreased number of reported incidents.

For this evaluation, the OPP IDS was utilized for pesticide incident data on the active ingredient glyphosate (PC Codes 103601, 103603, 103604, 103605, 103607, 103608, 103613, and 417300). The incident data system records incidents in one of two modules: Main IDS and Aggregate IDS. Main IDS contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics. This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one active ingredient (as opposed to pesticide products with multiple active ingredients) are considered to provide more certain information about the potential effects of exposure from the pesticide. The higher severity outcomes include:

- H-A (death): If the person died;
- H-B (major): If the person alleged or exhibited symptoms which may have been life-threatening, or resulted in adverse reproductive effects or in residual disability; and
- H-C (moderate): If the person alleged or exhibited symptoms more pronounced, more prolonged or of a more systemic nature than minor symptoms, usually some form of treatment of the person would have been indicated, symptoms were not life threatening and the person has returned to his/her pre-exposure state of health with no additional residual disability.

Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries. The less severe human incidents include:

- H-D (minor): If the person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involve skin, eye or respiratory irritation; and
- H-E/H (unknown or no effects): If symptoms are unknown, unspecified or are alleged to be of a delayed or chronic nature that may appear in the future.

For the Main IDS, from January 1, 2008 to September 11, 2013, there are 502 cases reported that involve the active ingredient glyphosate. Of these 502 cases, there are 212 cases reported for the single chemical glyphosate in the database that occurred in the United States.[1] Summaries of these incidents are recorded in Appendix A. There was one death due to suicide, 6 suicide attempts, 2 suspected suicide attempts, and three malicious intent incidents which were not reviewed further for symptoms and are not included in the severity totals. There were also two incidents reported as lawsuits to IDS that were not considered in this report.

In addition to the suicide, there were two deaths reported. Upon further review these two reported deaths cannot be substantiated as being related to glyphosate. In one case, the death

[1] There were 16 events reported that occurred outside of the United States (5-Canada, 5-Brazil, 2-Argentina, 1-United Kingdom, 1-Jamaica, 1-Malawi, 1-Mozambique) that were not reviewed. Foreign incidents are not reviewed in detail because of the potential differences in the exposure patterns, use practices, and product formulation.

was reported by a third party with no further details. In the other case, a woman reported her husband and a neighbor both died of tumors. She reports that both she (major severity) and her husband (death) were exposed to Roundup three years before, and both developed tumors; however, the exposure to Roundup is unclear in the incident report.

One hundred and ninety nine cases were reviewed further for severity, exposure scenario, and reported symptoms. Nine of these incidents classified as majors; 185 incidents were classified as moderates; 2 incidents were classified as minor and 1 was classified as no effects. [2] The nine major severity incidents mostly involved applicators (4 were home owner mixer/loader/applicator and 2 were applicators (unknown if home or agricultural), 1 is nonagricultural occupational exposure and 2 are unknown exposure scenario.

Homeowner mixing/loading and/or applying resulted in the most (46%) reported exposures (most of these incidents occurred due to leaks, spills, splashes, mist and product blowback during mixing loading or applying (n=46), or equipment malfunction (n=12)) followed by post application exposure (14%). There were 9 exposures to children ages 11 years old and younger. These children were exposed through post application exposure or due tampering with the product, or accidental exposure. A summary the exposure scenario counts reported to Main IDS is provided in Table 1. The incident narratives for these incidents are provided in Appendix 2.

Table 1. Exposure Scenario Frequency of incidents reported to Main IDS (2008-2013)

Exposure Scenario	Number of reported incidents (%)
Home owner mixer/loader/applicator	90 (46)
Post application exposure	27 (14)
Unknown	20 (10)
Applicator exposure (unknown if homeowner of occupational)	17 (9)
Drift	12 (6)
Child exposures	9 (5)
Occupational application exposure	6 (3)
Accidental ingestions (adult)	5 (3)
Dermal contact (not applying)	4 (2)
Ingestion of treated fruit	2 (1)
Occupational mixing/loading	2 (1)
Non-agricultural occupational exposure	1 (0.5)
Smoked product in marijuana	1 (0.5)
Indoor use	1 (0.5)
Total	197[a]
[a]This total does not include the two death incidents which are described above.	

[2] Minor severity incidents and "no effects" incidents are typically reported to the Aggregate IDS, but do occasionally get reported to the Main IDS. For glyphosate, there are 6054 more minor severity incidents and 89 incidents with no or unknown effects reported to Aggregate IDS.

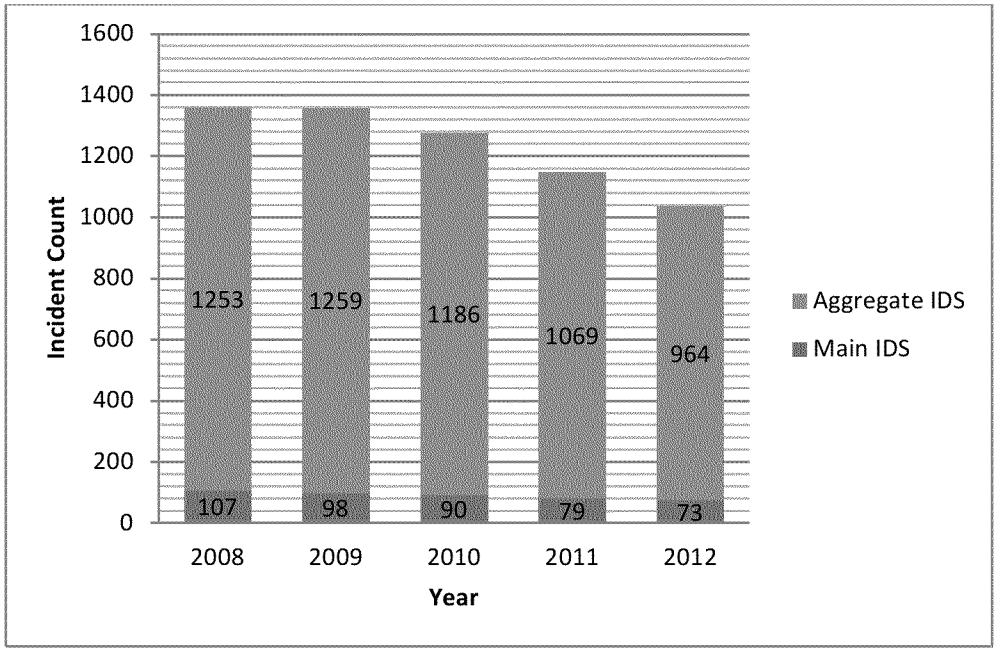
Based on the IDS reports, symptoms most often reported were dermal (n=72), neurological (n=70), respiratory (n=37), ocular (n=27), gastrointestinal (n=24), and cardiovascular (n=7). Note that a patient could exhibit multiple symptoms. Dermal symptoms reported include hives, swelling, rash, burning sensation, blotches, redness, peeling skin, and itchiness. Neurological symptoms reported include shaking, muscle cramps, diaphoresis, headaches, paresthesia, ataxia, disorientation, and dizziness. Respiratory symptoms reported included wheezing, coughing, sinus infection, nasal discharge, sore throat, and shortness of breath. Ocular symptoms reported were burning eyes, eye irritation and swelling, eye redness, foreign body sensation and vision problems. Gastrointestinal symptoms reported were nausea, diarrhea, vomiting, and abdominal pain. Cardiovascular symptoms reported include low blood pressure, chest tightness, chest pain, and heart attack.

In Aggregate IDS, queried from January 1, 2008 to May 8, 2013, there are 6143 incidents involving glyphosate. Because it falls within the categories reported as counts (which includes minor, unknown or no effects), there is no unique report that provides details about the incident and single chemical incidents are not distinguished from multiple chemical incidents; however, in general a high frequency of incidents indicates there is a high potential for exposure or elevated acute toxicity and vice versa.

Most (92%) of the incidents reported to IDS involving glyphosate were either minor severity (n=6054) or no or unknown effects (n=89). For the minor incidents, this means that a person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involved skin, eye or respiratory irritation. For the no/unknown effects, this mean that symptoms are unknown, unspecified or are alleged to be of delayed or chronic nature that may appear in the future.

The glyphosate incidents trend over time, from 2008 to 2012, was reviewed. The number of reported incidents appears to have decreased since 2008 (Figure 7).

Figure 7. Number of Glyphosate Incident per Year (2008 to 2012) Reported to IDS



The most often implicated glyphosate products in Main IDS are:

- Honcho Herbicide (Reg. No. 524-445) (n=88)
- Roundup Weed & Grass Killer Ready-To-Use Poison Ivy and Tough Brush Killer (Reg. No. 71995-23) (n=20)
- Roundup Weed & Grass Killer Ready-To-Use (Reg. No. 71995-32) (n=19).

In Aggregate IDS the main often implicated products are:

- Roundup Weed & Grass Killer Ready-To-Use Plus (Reg No. 71995-33) (n=1397)
- Roundup Weed & Grass Killer Concentrate Plus (Reg. No. 71995-29) (n=746)
- Roundup Herbicide (Reg. No. 524-445) (n=628)
- Roundup Weed & Grass Killer Ready-To-Use Poison Ivy and Tough Brush Killer (Reg. No. 71995-23) (n=390), and
- Roundup Weed & Grass Killer Ready-To-Use (Reg. No. 71995-32) (n=341).

Roundup Weed & Grass Killer Ready-To-Use Plus (Reg No. 71995-33) was implicated the most often in IDS (n=1397). This product is used to kill weeds and grasses in places, such as on patios, walkways, and driveways, (gravel, or mulch beds) in flower beds and vegetable gardens, around shrubs and trees, along fences and foundations. This is likely due to the high volume of use of this product. All the resulting incidents are minor severity.

b. National Pesticide Information Center (NPIC) (2007-2013)

The National Pesticide Information Center or NPIC is a cooperative effort between Oregon State University and EPA which is funded by EPA to serve as a source of objective, science-based pesticide information and respond to inquiries from the public and to incidents. NPIC functions nationally during weekday business hours through a toll-free telephone number in addition to the internet (www.npic.orst.edu) and email. Similar to Poison Control Centers, NPIC's primary purpose is not to collect incident data, but rather to provide information to inquirers on a wide range of pesticide topics, and direct callers for pesticide incident investigation and emergency treatment. Nevertheless NPIC does collect information about incidents (approximately 4000 incidents per year) from inquirers and records that information in a database. NPIC is a source of national incident information but generally receives fewer reports than IDS. Regardless, if a high frequency is observed in IDS, NPIC provides an additional source of information to see whether there is evidence of consistency across national data sets or possibly duplication and additional information about the same incident(s).

From 2007 to July 2013, 173 glyphosate incidents were reported to NPIC. NPIC estimates a certainty index as to whether an incident (including reported symptoms) was either definitely, probably, possibly, or unlikely to have been caused by the reported exposure to a pesticide, or whether the incident was unrelated to pesticides or if the incident was unclassifiable. Of the 173 reported incidents, 34 were reported as symptomatic and classified as definitely, probably, or possibly related to the glyphosate exposure and 55 cases were unclassifiable. Of these 55 unclassifiable cases, 53 were asymptomatic and 2 were reported as unknown symptoms. Of the 173 reported incidents, 82 were classified by NPIC as unlikely to have been caused by glyphosate. There were two suicide attempts which were not further reviewed. The Agency further reviewed the 89 incidents that were classified as definite, probable, possible and unclassifiable.

Of the 89 reported incidents reviewed by the Agency, homeowner mixing/loading and/or applying resulted in the most (n=42) reported exposures. Of these 42 exposures, most (n=26) occurred due to leaks, spills, splashes and product blowback during mixing loading or applying, or (n=11) equipment malfunction. Of the 89 reviewed incidents, the next most reported exposures were due to childrens exposures and drift (both 19%). A summary of the exposure scenario counts reported to NPIC is provided in Table 2.

Table 2. Exposure Scenario Frequency of Incident Reported to NPIC (2007-2013)

Exposure Scenario	Number of reported incidents (%)
Home owner mixer/loader/applicator	42 (47%)
Child exposures	15 (19%)
Drift	15 (19%)
Dermal contact (not applying)	6 (7%)
Occupational applicator	4 (4%)
Homeowner post application exposure	3 (3%)
Adult accidental ingestion	2 (2%)
Ate treated food from garden	1 (1%)
Unknown exposure	1 (1%)
Total	89

The symptoms most often reported to NPIC were respiratory (n=11), ocular (n=11), neurological (n=9), dermal (n=8), and gastrointestinal (n=5). Note that a patient could exhibit multiple symptoms. Respiratory symptoms reported included difficulty breathing, nasal discharge, nose irritation, and throat irritation. Ocular symptoms reported were red and irritated eyes, burning eyes, stinging eyes, blurry vision. Neurological symptoms reported include headaches, loss of balance, altered taste, dizziness, and Paresthesia. Dermal symptoms reported include rash, burning sensation, and redness. Gastrointestinal symptoms reported were nausea, diarrhea, and vomiting.

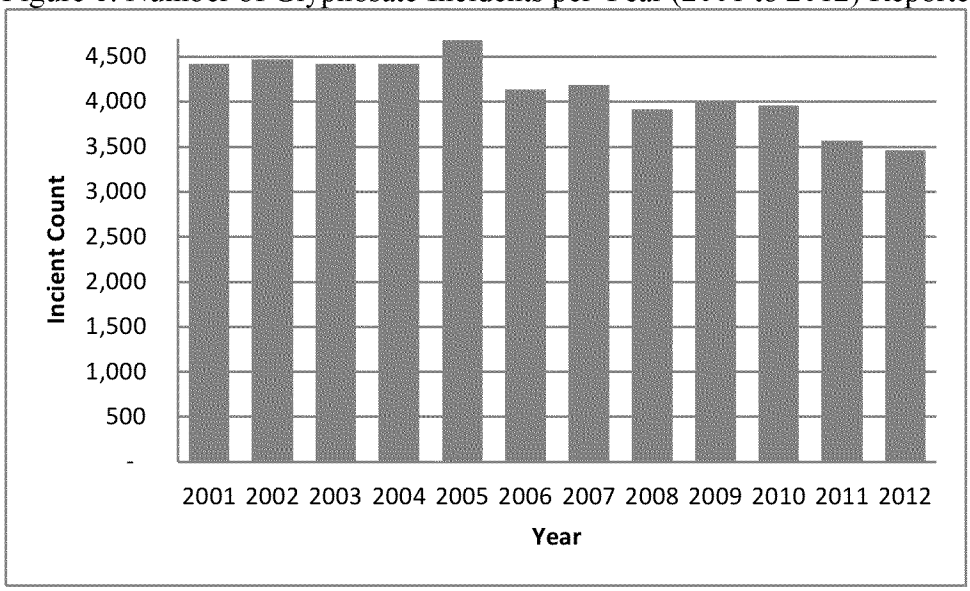
c. American Association of Poison Control Centers (2001-2012)

The American Association of Poison Control Centers (AAPCC) is a non-profit, national organization founded in 1958 that represents the poison control centers of the United States and the interests of poison prevention and treatment of poisoning. All of the calls to a poison control center are managed by a medical professional trained to answer questions about poisons. Additionally, AAPCC reports provide clearly summarized information on pesticide incidents within the context of other poisoning events.

AAPCC produces an annual summary report giving statistics and information on all the poisonings reported to PCCs in a calendar year (http://www.aapcc.org/annual-reports/). Glyphosate is included in the AAPCC annual summary and Agency examined the data from 2001 to 2012. According to the AAPCC 2012 annual report, glyphosate products ranked first with 3,464 single exposures among the reported human herbicide exposures (total reported herbicide exposures were 4717). There were 3257 unintentional exposures, and 875 cases were

to children 5 years old and younger.[3] A review of the AAPCC incident trend for glyphosate from 2001 to 2012 suggests a decrease in reported glyphosate incidents from 2005 to present (Figure 8).

Figure 8. Number of Glyphosate Incidents per Year (2001 to 2012) Reported to AAPCC



d. California Pesticide Illness Surveillance Program (PISP) (2005-2010)

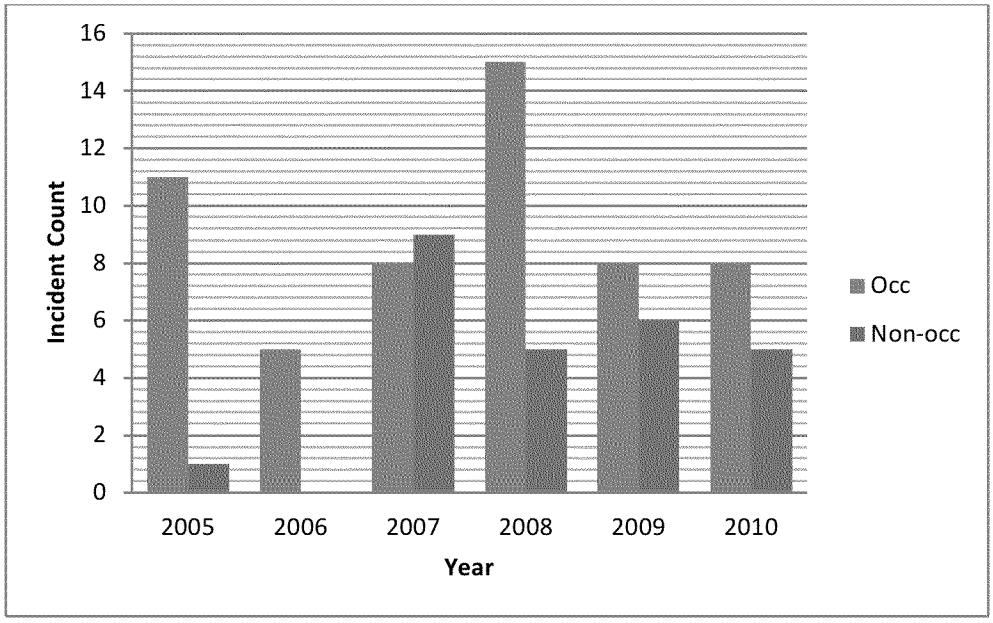
The California Pesticide Illness Surveillance Program (PISP) maintains a database of pesticide-related illnesses and injuries. Case reports are received from physicians and via workers' compensation records. The local County Agricultural Commissioner investigates circumstances of exposure. Medical records and investigative findings are then evaluated by DPR technical experts and entered into an illness registry.

PISP contains both residential and occupational pesticide incidents. PISP has limited coverage (only California) and is not particularly useful for trend over time information. However, the incident information is entered by professionals with expertise in pesticides, with extensive follow-up on each reported case so there is a high level of confidence in the information provided for each reported incident.

Eighty one cases were reported to PISP between 2005 and 2010 that involve the single reported active ingredient, glyphosate. All of these cases were classified as having a definite, probable or possible relationship with glyphosate. A total of 55 were occupational cases and 26 were non-occupational cases (Figure 9). The majority of cases (both occupational and non-occupational) occurred in a non-agricultural setting (N=56) such as landscaping or residential; 24 cases occurred in agricultural settings and in one case setting was unknown.

[3] 2012 Annual Report of the American Association of Poison Control Centers ' National Poison Data System (NPDS): 30th Annual Report
https://aapcc.s3.amazonaws.com/pdfs/annual_reports/2012_NPDS_Annual_Report.pdf

Figure 9. Number of Glyphosate Incidents per Year (2005 to 2010) Reported to PISP



The glyphosate exposure scenarios in PISP were as follows:

- 31 cases were related to the handling of application equipment, including:
    - 18 cases were related to application equipment leaks or malfunctions
    - Nine cases were related to problems while loading equipment or over-pressurizing equipment
    - Four cases involved the cleaning or repair of application equipment
    - Of these 31 equipment handling exposures, 22 cases were sprayed or splashed in the eyes or face while working with the application equipment. Eight of these cases were product handlers who were either failed to wear protective eyewear or removed their protective eyewear to load or repair the pressurized equipment and were splashed in the face and eyes (other cases may have had similar PPE issues but were not specifically cited in the report).
- Eight cases were the result of either drift (worker or bystander) or an application made while windy (exposing the handler)
- Nine cases were due to the ingestion of the product, five of which were accidental and four were intentional

- Five cases resulted from various accidents, such as vehicle problems
- Three cases involved toddlers who found the product and sprayed themselves
- Ten cases involved other various occupational exposure circumstances
- Eight cases involved other various bystander exposure circumstances
- Four cases involved other various homeowner exposure circumstances
- Three cases had unknown or unclear exposure scenarios

Symptoms Reported

Note that a patient could exhibit multiple symptoms. The most commonly reported symptom was eye irritation (n=39), followed by dermal irritation (n=37). Fourteen cases reported gastrointestinal symptoms, including vomiting, nausea, and diarrhea. Eleven cases reported respiratory symptoms including cough, wheeze, and shortness of breath. Nine cases reported a neurological symptom including headache, anxiety and dizziness. One case reported cardiovascular symptoms (Table 3).

Table 3. PISP 2005-2010: Health Effects for Glyphosate Cases

Health Effect*	Frequency
Ocular	39
Dermal	37
Gastrointestinal	14
Respiratory	11
Neurological	9
Cardiovascular	1
* Cases may report multiple health effects	

The most notable exposure pattern in the PISP data is the splashes to the eye/face during equipment handling. Appropriate PPE use, particularly protective eyewear, and equipment pressurization were important contributing factors for the glyphosate incident reports in PISP.

e. SENSOR-Pesticides (1998-2009)

The SENSOR-Pesticides database covers 11 states from 1998-2009, although reporting varies from state to state. Cases of pesticide-related illnesses are ascertained from a variety of sources, including: reports from local Poison Control Centers, state Department of Labor workers' compensation claims when reported by physicians, reports from State Departments of Agriculture, and physician reports to state Departments of Health. Although both occupational and non-occupational incidents are included in the database, SENSOR focuses on occupational pesticide incidents, and is of particular value in providing that information. A state SENSOR contact specialist attempts to follow-up with cases and obtains medical records to verify symptoms, circumstances surrounding the exposure, severity, and outcome. Using standardized protocol and case definitions derived from poison center reporting, SENSOR coordinators at State Departments of Health enter the incident interview description provided by the case, medical report, physician and patient into the SENSOR data system. The SENSOR data system is accessible to participating states and EPA.

A query of SENSOR-Pesticides 1998-2009 finds a total of 834 case reports involving glyphosate (pc codes 103601, 103603, 103604, 103605, 103607, 103608, 103613, 417300); of these, 505 involve a single active ingredient (ai). The 505 single ai cases, stemming from 495 events (no large multiple exposure events were identified), will be reviewed for this analysis. Six cases were high in severity, 57 were moderate in severity and 442 were low in severity (Table 4). Case narratives for all high and moderate severity cases are provided in Appendix 3.

Table 4. SENSOR-Pesticides 1998-2009 Glyphosate Cases by Severity (N=505)

Severity	Incident Count
Fatal	0
High	6
Moderate	57
Low	442
Total	505

Occupational and Nonoccupational[4]

- 272 cases were work-related
- 186 cases were not work-related
- 47 cases were unknown/unclear

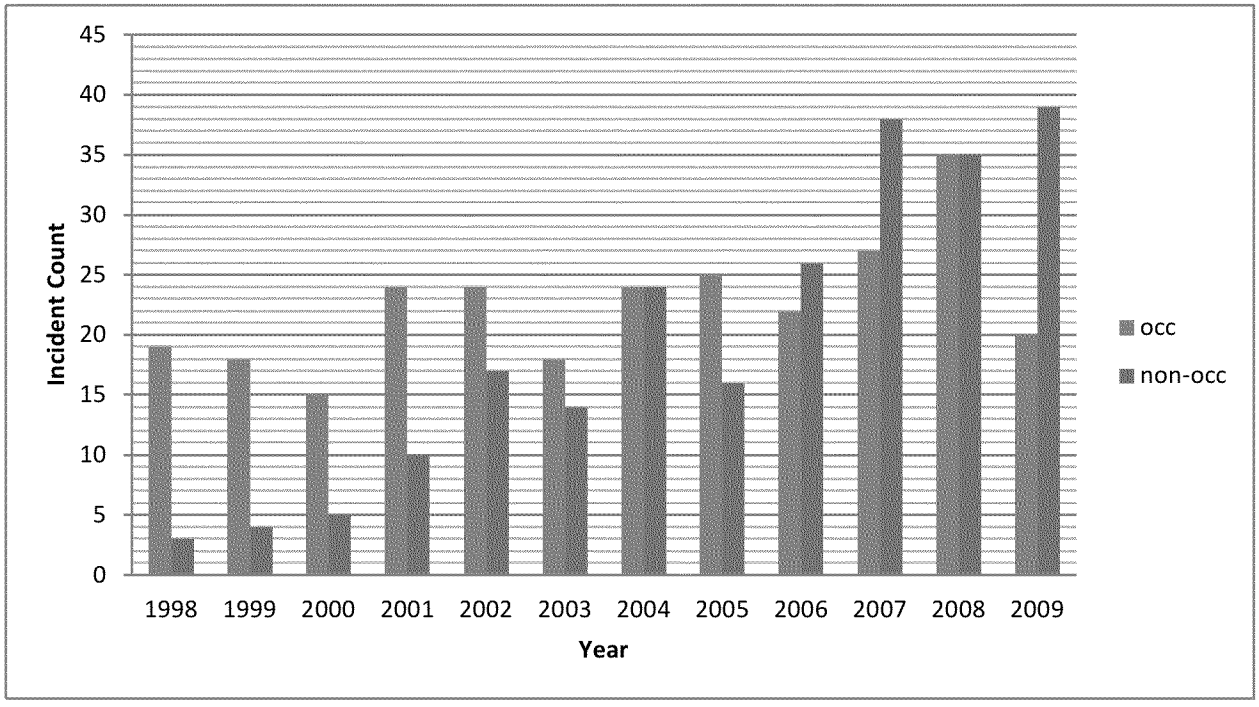
[4] SENSOR-Pesticides defines work-related cases as those illness and injuries occurring at the case's place of work.

Overall, occupational case reports involving glyphosate appeared to be increasing until 2008 and non-occupational case reports appear to be increasing over time. This trend is shown in Table 5 and the corresponding Figure 10, broken down by occupational and non-occupational case reports. The increase in non-occupational case reports may be reflective of increased SENSOR state capacity to collect non-occupational pesticide surveillance data.

Table 5. SENSOR Glyphosate Incident Count per Year (1998-2009)

Year	Occupational	Non-Occupational/ Unknown	Total
1998	19	3	22
1999	18	4	22
2000	15	5	20
2001	24	10	34
2002	24	17	41
2003	18	14	32
2004	24	24	48
2005	25	16	41
2006	22	26	48
2007	27	38	65
2008	35	35	70
2009	20	39	59
Year blank	1	2	3
Grand Total	**272**	**233**	**505**

Figure 10. Number of Glyphosate Incident per Year (1998 to 2009) Reported to SENSOR-Pesticides



Reported Symptoms

Dermal symptoms were most frequently reported (n=244) followed by ocular symptoms (n=194). The breakdown of all the symptoms are included in Table 6.

Table 6. SENSOR-Pesticides 1998-2009: Reported Health Effects for Glyphosate Cases

Health Effect*	Frequency
Dermal	244
Ocular	194
Nervous System	160
Gastrointestinal	157
Respiratory	148
Miscellaneous	48
Cardiovascular	23
Renal	5
* Cases may report multiple health effects	

Route of Exposure*
Dermal-244
Inhalation-150
Ingestion-57
Ocular-156
Unknown-32
*Case may have been exposed via multiple routes.

Multiple Exposure Events
No large multiple case exposure events were found. In Florida in 2004, four cases were exposed to Roundup after their neighbor applied it at the fence line and it subsequently drifted onto the property next door. Three were low in severity and one was moderate in severity.

Exposure Information
The most common single ai glyphosate exposure, responsible for 50% of cases, involved the application of the product. A closer review of the high and moderate severity case narratives (n=63) was conducted. Of the 63 high and moderate cases, 19 were missing case descriptions. Seventeen of the cases with missing narratives are California cases from 1998-2003. Of the remaining 44 high/moderate severity cases with case narratives provided: 16 were exposed while applying the product, eight involved equipment problems while handling the product (leaks, breaks, etc), six various exposure scenarios occurring at non-agricultural workplaces (such as landscape, Walmart), six resulted from ingestion of the product (three of these ingestion cases were high severity), four bystander exposures, two spills while mixing the product, and one child who handled the product. Among the high/moderate severity cases, ocular symptoms were most frequently reported (n=28); followed by dermal (n=25). A summary of case narratives for all moderate and high severity cases are provided in Table 7 below.

Table 7. Case Activity at Time of Exposure in SENSOR-Pesticides (1998-2009)

Code	Activity	Frequency
1	Applying	253
99	Unknown	60
10	Routine outdoor living	55
8	Routine work incl. fieldworkers	52
9	Routine indoor living	36
2	Mixing/loading	15
5	Any combination of 1-4	11
3	Transport or disposal	9
98	Not Applicable	8
4	Repair or maintenance	6
6	Manufacture or formulation	0
7	Emergency response	0
11	Application to self or another	0

Drift Cases

There were 59 glyphosate cases reported that related specifically to drift.

Child Exposures

There were 48 cases reported that involved children under the age of 18 (42 of which were 12 and under) (Tables 8 and 9). In most cases (23), children 6 years old and younger were exposed due to ingestion or tampering with the product.

Table 8. Number of reported glyphosate incidents to children in SENSOR-Pesticides

Age of Child	Incident Count
6 and under	33
7 to 12	10
13 to 17	5
Total	48

Table 9. Age 6 and under case scenarios

Exposure Scenario	Incident Count
Ingestion	12
Child Tampering with product[a]	11
Routine Application	7
Unknown	2
Spill	1
Total	33
[a]Child tampering excludes ingestion, generally involves child spraying self with product resulting in ocular or dermal exposure.	

f. Acute Glyphosate Poisoning Incident Summary

HED previously reviewed glyphosate in 2009 (*Updated Review of Glyphosate Incident Reports*, M. Hawkins and J Cordova, 03/12/2009). From the years 2002 to March 2009, 289 incidents involved products containing the single chemical glyphosate in Main IDS. HED found that "the IDS query resulted in a moderately large number of case reports which warrants searching the following databases for consistency and reproducibility of the poisoning incident data: the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS), the California Pesticide Illness Surveillance Program, and the National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR)." The general findings and conclusions from HED's current review of IDS (for years 2008-2013) agree with those from this previous HED review. HED found a moderately large number of incidents reported to IDS (212 cases reported for the single chemical glyphosate in Main IDS and an additional 6143 incidents involving glyphosate in Aggregate IDS) and analyzed three additional databases and the AAPCC Annual Reports.

HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report, and the other databases and medical literature reviewed. These health effects primarily include dermal, ocular, and respiratory effects. HED did not identify any

aberrant effects outside of those anticipated. While inconvenient for those who suffer adverse health effects, effects are generally mild/minor to moderate and resolve rapidly.

The incident data available from IDS and NPIC suggest that homeowner mixing/loading/ applying (usually due to human errors and container leaks) are responsible for almost half of the reported incidents. SENSOR-Pesticides incident data are consistent with IDS and NPIC, also suggesting that application of glyphosate results in the most reported incidents (50%). However, the SENSOR-Pesticide incidents include both residential and occupational incidents. The incident data available from CA PISP suggests that occupational handling of equipment is responsible for most incidents due to equipment leaks and malfunction.

All of the databases showed the occurrence of childrens' exposures (ranging from 5% to 27% of total cases). Based on the data in SENSOR, IDS, and NPIC, it appears that the childrens' exposures are due to postapplication exposure, accidental ingestion, and tampering with the product. Ocular exposures and symptoms were reported in all of the databases, to both occupational and nonoccupational users, as a result of splash to the face or touching their eyes with the product on their hands. These symptoms primarily included eye irritation, redness, burning and blurred vision.

Trends over time data from IDS (2008 to 2012), PISP (2005 to 2010), SENSOR-Pesticides (1998 to 2009) and AAPCC (2001 to 2012) data were reviewed. Based on IDS and AAPCC, which are primarily non-occupational cases, incidents appear to be decreasing over time. CA PISP data represents both occupational and non-occupational incidents. This data appears to be relatively steady over time. The SENSOR-Pesticide data also represent both occupational and non-occupational cases. For this data, occupational case reports involving glyphosate appeared to be increasing until 2008 and non-occupational case reports appear to be increasing over time. The increase in non-occupational case reports may be reflective of increased SENSOR state capacity to collect non-occupational pesticide surveillance data.

4. CHRONIC DISEASE EPIDEMIOLOGY

In this section, HED discusses the available evidence concerning the chronic health effects of glyphosate exposure in the human population. Environmental epidemiology studies are designed to evaluate whether there is evidence of an increased (or decreased) risk of disease in relation to a specific environmental risk factor such as pesticide exposure. For this report, HED/TEB identified several published, peer reviewed epidemiology studies concerning exposure to glyphosate. A wide variety of cancer and non-cancer health outcomes are included in this analysis.

a. Literature Review Methodology

In preparing this Tier II review of environmental epidemiology data related to glyphosate exposure, HED queried publis6hed, peer-reviewed literature. Appendix 4 describes the methods reviewers utilized to identify, to select, and to evaluate the open literature studies. These methods are in accordance with the OPP Guidance on Open Literature Reviews[5]. Briefly, reviewers developed a comprehensive search string for use in both PubMed and Web of Science, two major biomedical searchable databases available to EPA scientists. Google scholar was also searched for additional unique research articles. Inclusion criteria were a direct epidemiologic measure of glyphosate (as opposed to all herbicides, or all phosphonic acid pesticides), and English language publication. Publication date was not restricted, but most articles were published 1990 to present. HED excluded articles that did not make an epidemiological risk estimate of glyphosate exposure in relation to an adverse health outcome (exposure only, acute toxicity only, experimental toxicology study, ecologic risk study, or other review or commentary), or were not full text articles (e.g., abstract only). There were 90 articles initially identified using the search string; of these, 59 were excluded and 31 included in full text review. Among the 31, only 10 were included in the review. Citation mapping added an additional 40 articles, of which 36 were derived from examination of two recent review articles (Mink, Mandel, Lundin, & Sceurman, 2011; P. J. Mink, J. S. Mandel, B. K. Sceurman, & J. I. Lundin, 2012), and four were identified using citation mapping techniques. An additional 5 articles were identified through the European Food Safety Authority pesticide epidemiology systematic review[6]. Therefore, there are 55 epidemiology studies included in the review of glyphosate evaluating both cancer and non-cancer chronic disease endpoints. A full description of literature review methodology is in Appendix 4 which includes a comprehensive listing of all articles identified and excluded based upon title and abstract review or full text evaluation, and a listing of the final 55 articles included in the review.

b. Summary of Glyphosate Epidemiology Literature

As discussed above, glyphosate is a non-selective herbicide registered for use on a variety of fruit, vegetable, and field crops, as well as for residential uses. Glyphosate can be applied pre- or post-emergence, or during the growing season. Therefore, given the number of use sites and the range of timing of application, the exposure potential is substantial. Available experimental evidence indicates that the acute and chronic toxicity of the pesticide is low by all routes of exposure, and well characterized as a result of submitted guideline studies. Glyphosate has been classified as a "Group E" chemical (evidence of non-carcinogenicity for humans), based upon lack of convincing evidence of carcinogenicity in adequate studies in two animal species (mice and rats). This section presents information pertaining to potential glyphosate toxicity in the human population. Epidemiology study review is important for several reasons: animal data are

[5] http://www.epa.gov/pesticides/science/literature-studies.html
[6] http://www.efsa.europa.eu/en/supporting/pub/497e.htm

not always good surrogates for health effects of chemicals in the human population; the exposure range in animal studies are typically much higher than experienced in "real world" human populations; and, human studies better reflect toxicity of the end-use product, as opposed to the active ingredient as well as exposure to a mixture of compounds. Considering this information, the results of observational studies in the human population are considered herein.

Studies included in this review evaluate both cancer and non-cancer health outcomes. Many of the studies included are from the Agricultural Health Study (AHS); however, there are several analyses from population-based case control studies in other parts of the Midwest, Canada and Europe. In addition, use of glyphosate in the control of illegal crops, *e.g.*, cocaine, is common in some parts of the world; there is one study included which was performed in South America (Columbia), in which this use is prevalent. It should be noted that, with only one exception, all the studies included in this review evaluate glyphosate *in addition to* several (dozen in some instances) other agricultural pesticides in relation to a potential health outcomes; glyphosate was only *a priori* identified as a compound of interest in the cohort study on glyphosate in the AHS in which glyphosate exposure and all cancer risks were compared. While there are several dozen studies included in this review, there may be only a few studies for each chronic health endpoint upon which to assess consistency of findings. Therefore, while the pesticide epidemiology database for glyphosate exposure is large in comparison to other active ingredients, it is still unfortunately limited in making causal inference for specific chronic disease outcomes. A summary of the observational studies of the human health effects of glyphosate is presented in this section.

b.1. Non-Cancer Effects

Epidemiological studies of the potential role of glyphosate, among other compounds, in the etiology of several non-cancer health effects are detailed in this sub-section.

b.1.1. Adverse Birth Outcomes

Several studies evaluated the role of pesticides and increased risk of adverse developmental and reproductive health outcomes. Pesticide exposure in relation to pregnancy complications such as gestational diabetes and increased time to pregnancy (TTP) as well as reproductive conditions like small-for-gestational age (SGA) and low birthweight are included in this section. Study authors also reviewed the potential role of pesticides in adverse birth outcomes such as neural tube defects (NTD), congenital malformations, and spontaneous abortion. A brief summary of these reports is included in this section.

Two studies evaluated time to pregnancy in relation to exposure to pesticides, hypothesizing that pesticide exposure may interfere with fecundability among those exposed. Within the Ontario Farm Family study, Curtis et al. (1999) reported some evidence of increased TTP (40% increase in TTP) among women exposed to glyphosate pre-conception (fecundability rate ratio (FRR)

0.61 (95% CI 0.24, 1.05)). Authors did not observe evidence of increased time to pregnancy given fathers exposure to glyphosate prior to conception (Curtis, Savitz, Weinberg, & Arbuckle, 1999). Authors state they identified no clear pattern of pesticide use in relation to TTP, but use of herbicides in general was more strongly linked to this outcome. The exclusion of sub-fertile and infertile women as well as potential exposure misclassification could have attenuated the effects estimates. However, unmeasured positive confounding and chance could explain positive findings. Authors did not identify any one pesticide as strongly linked to TTP in this study, indicating further research is needed. In a separate investigation using ecologic exposure assessment methods, authors examined use of Roundup (glyphosate end use product) by illicit drug production area. Sanin et al (2009) and colleagues reported some evidence of reduced time to pregnancy among women who reside in areas of Columbia (South America) in which illicit drug eradication programs using glyphosate are of the greatest intensity (FRR 0.15 (0.12, 0.18)) (Sanin, Carrasquilla, Solomon, Cole, & Marshall, 2009). Both studies investigating TTP in relation to pesticide use have uncertainties, making it difficult to draw firm conclusions. The indirect (and ecologic) nature of the pesticide exposure assessment in both evaluations dictate further follow-up before a link with this reproductive health endpoint can be established.

HED also identified studies on pregnancy outcomes such as pre-term delivery and small-for-gestational age in relation to pesticide use. Across these studies, there is little evidence of a role for glyphosate. Savitz et al. (1997) reported a non-statistically significant association between glyphosate use and preterm delivery (OR (95% CI) 1.5 (0.8, 2.7), and no link with SGA (OR (95% CI) 0.80 (0.20, 2.3)) (Savitz, Arbuckle, Kaczor, & Curtis, 1997). However, the authors acknowledge the study requires replication as there is insufficient evidence to suggest a role for any specific pesticide in this study. Garry et al. (2002) evaluated pesticide use and male:female sex ratio in an agricultural area of the U.S., but did not report any glyphosate-specific risk estimate because there was no significant exposure-response relation with this chemical (Garry et al., 2002).

While other pesticide epidemiology studies have reported an association with low birth weight and pesticide exposure (Whyatt et al., 2004), Sathayanarayana et al. (2010) did not observe such a link when considering glyphosate use in the AHS cohort (Sathyanarayana et al., 2010). In the cross-sectional study, authors compared lifetime glyphosate use (as reported by female spouses of male pesticide applicators) and range of pregnancy time period. Other pesticides were marginally linked to low birth weight, but glyphosate was not associated with this outcome. Further Saldena et al. (1999) performed a cross-sectional analysis of pesticide use and gestational diabetes in the AHS cohort. Among 11,273 pregnancies reported among women enrolled in the cohort study, authors did not observe a relation between gestational diabetes and self-reported, ever-use of glyphosate during the first trimester of the most recent pregnancy. While errors in the timing of exposure (misclassification) and residual confounding could have reduced the observed effect estimates, the observation of a link with some pesticides, but not glyphosate, suggest the herbicide may not play a role in GD, based upon the evidence in this study.

There were several studies of birth malformations in relation to pesticide use including glyphosate. Rull et al examined the relation between glyphosate and other pesticides and birth certificate reported incidence of neural tube defects (Rull, Ritz, & Shaw, 2006). Cases (731) were births between 1987-1991 in CA, and pesticide exposure was measured as maternal residential proximity to an agricultural field treated with specific pesticides. Authors reported non-statistically significantly elevated (50%) risk of NTD among glyphosate exposed women, adjusting for education, ethnicity, peri-conception smoking and vitamin use. Results were attenuated upon mutual adjustment for exposure to other pesticides (OR (95% CI) 1.4 (0.8, 2.5)). Authors pooled two population-based case control studies to increase the number of birth defect cases included in the study. However, major findings from this pooled analysis related to other pesticides (methomyl, benomyl), and not glyphosate. The non-significant result could be explained by exposure misclassification (which would not likely be differential since residential address and not self-report was used in exposure assessment), residual confounding by factors negatively related to both pesticide use and NTD, or small number of glyphosate exposed cases. Garcia et al. (1998) initially identified a positive association between congenital malformations and glyphosate (OR (95% CI) 1.23 (0.59, 2.56), but the association attenuated considerably upon mutual adjustment for other risk factors including spontaneous abortion, drug use, smoking, education, occupational exposure to other pesticides, and age (OR (95% CI) 0.94 (0.37, 2.56) (Garcia, Benavides, Fletcher, & Orts, 1998). Arbuckle et al. (2001) reported non-statistically significantly elevated risk of spontaneous abortion among women who were exposed to glyphosate pre-conception (OR (95% CI) 1.7 (1.0, 2.9)) and post-conception (OR (95% CI) 1.4 (0.80, 2.5))(Arbuckle, Lin, & Mery, 2001). There were many strengths of this study including the ability to measure exposure in the pre- and post-conception time periods; however authors of this study urge caution in the interpretation of results because many different statistical tests were performed, and exposure misclassification is possible. Glyphosate exposure was among the key findings of the study (atrazine and carbaryl also associated with spontaneous abortion in this study). Considering the totality of the scientific data concerning adverse birth outcomes, there is little overall evidence of a role for glyphosate at this time.

b.1.2 Respiratory Effects

Within the AHS, authors have made several evaluations of respiratory health effects and pesticide exposure including asthma, chronic bronchitis, rhinitis and wheeze. Each investigation utilized a cross-sectional study design; however, given the study was with the prospective AHS and the use of certain analytic methods, concerns about temporal bias (exposure did not precede onset of respiratory health effect) are somewhat ameliorated. In addition, each study was hypothesis-generating in nature such that all pesticides within the AHS were measured in association with incidence or prevalence of these health effects. Across these studies, there were some observations of positively elevated risks of adverse respiratory health in association with glyphosate use; however, for the most part, other compounds were more strongly associated with respiratory health. Given the hypothesis-generating nature of these studies, many statistical tests

performed and the potential for unmeasured, positive confounding bias that may explain outcomes, more research is needed to clarify whether glyphosate truly plays a role in respiratory health.

Hoppin et al. (2008, 2009) evaluated adult-onset asthma and prevalence of atopy in both men and women enrolled in the AHS. Atopy is the presence of other allergic conditions such as hay fever and eczema. Authors observed elevated odds of asthma among those with and without atopy in both men and also women among those who report use of glyphosate. Results were similar for men and women and did not statistically differ between those with and without atopy (Women: atopic asthma: OR (95% CI) 1.31 (1.02, 1.67); non-atopic asthma: OR (95% CI) 1.13 (0.92, 1.39), p-value 0.40; Men: atopic asthma: OR (95% CI) 1.37 (0.86, 2.17), non-atopic asthma: OR (95% CI) 1.15 (0.87, 1.51)) (Hoppin et al., 2008; Hoppin et al., 2009). Glyphosate was one of two herbicides among 11 different herbicides tested that were statistically significantly association with asthma in this study and chance may therefore play a role; other pesticides were more strongly related to asthma in this study. Rhinitis, or runny nose, was marginally, but significantly, associated with glyphosate use among both private but not commercial applicators (odds at least one rhinitis episode in past year: 1.09 (1.05, 1.13); odds 13+ episodes rhinitis in past year: 1.14 (1.07, 1.21), global p=0.001)) (Slager et al., 2009; Slager et al., 2010). The authors did not observe a relation with chronic bronchitis among either men (OR 0.99 (95% CI (0.82, 1.19)) or farm women (1.07 (95% CI (0.89, 1.29)) (Hoppin et al., 2007; Valcin et al., 2007). There is little evidence of a role for glyphosate in the prevalence of wheeze among either private or commercial pesticide applicators, and risk estimates attenuate considerably upon mutual adjustment for pesticides and chlorimuron-ethyl specifically (Hoppin, Umbach, London, Alavanja, & Sandler, 2002; Hoppin et al., 2006). While these authors note an elevated odds of wheeze among glyphosate users who are not also asthmatics (OR (95% CI) 1.5 (1.1, 2.1)), researchers also note that a healthy worker effect in which applicators with asthma or wheeze avoid chemical exposure, making the effect estimate for non-asthmatics artificially higher than asthmatics (Hoppin et al., 2002). These studies indicate a possible role for pesticides in respiratory health; however glyphosate is not strongly suggested as a risk factor based upon these data.

Overall, while some significantly elevated odds of adverse respiratory health outcomes were observed in relation to glyphosate use, the number of statistical tests, the hypothesis-generating nature of these studies, and the limited ability to co-adjust for other pesticides (particularly in studies of women) render the database insufficient to make a determination of the role of glyphosate in these outcomes.

b.1.3 Other Non-Cancer Effects

HED also identified epidemiology studies of other non-cancer health effects in relation to pesticide use including glyphosate exposure. Endpoints include auto-immune (rheumatoid arthritis) and endocrine (diabetes) effects, dysfunction of the cardiac (myocardial infarction) and

neurological (Parkinson's disease) systems, respiratory health, and retinal degeneration. DeRoos et al. (2005) examined the association between pesticide use including glyphosate and the incidence of rheumatoid arthritis (RA) in a nested case control study in the AHS. Among 135 RA cases and 675 matched controls, authors did not observe a link with RA by self-reported glyphosate use (odds ratio (OR (95% CI) 1.2 (0.8, 1.8)), and there was no difference in risk by study state (IA or NC) (De Roos, Cooper, Alavanja, & Sandler, 2005). Given the cross-sectional nature of the study, disease initiation could have preceded pesticide use (temporal bias) affecting the risk estimate (under-estimate if prevalent cases mixed with new cases). However, authors conclude on the basis of this study that other farm exposures excluding pesticide use may be more strongly related to RA etiology. In another study within the AHS, Kirrane et al. (2005) examined retinal degeneration (RD) among wives of enrolled pesticide applicators in relation to pesticide use. Among 31,173 women enrolled in the study, authors did not observe an association between self-reported, ever-use of glyphosate and RD (OR (95% CI) 1.1 (0.8, 1.5)) (Kirrane et al., 2005).

Kamel et al. (2007) performed an analysis of both incident and prevalent Parkinson's disease (PD) in relation to pesticide use among AHS participants. Among 79,557 private and commercial pesticide applicators, authors identified 83 prevalent and 78 incident cases of PD. PD status was measured as a result of participants self report of a physician diagnosis of the condition (no confirmation). Pesticide use was also measured using the AHS self-report questionnaire from which lifetime exposure days was calculated. Adjusting for age, state and type of applicator (or spouse of applicator), authors did not observe a significant, positive association between glyphosate and either incident (OR (95% CI) 1.1 (0.6, 2.0), or prevalent PD (OR (95% CI) 1.0 (0.6, 1.7)) (Kamel et al., 2007).

Similarly, a study of cardiac effects in relation to pesticide use in the AHS did not identify any links with glyphosate. Because risk factors for heart attack (MI) differ greatly between men and women, authors examined each group in separate studies. Controlling for the age, state, smoking, BMI, and the use of other pesticides (only among men), authors did not observe any association between incident MI or mortality due to MI among either male or female participants in the AHS with glyphosate – relative risks were the null value (1.0) (Dayton et al., 2010; Mills, Blair, Freeman, Sandler, & Hoppin, 2009).

AHS authors also examined diabetes in relation to pesticide use, and did not observe evidence of an association with glyphosate (OR (95% CI) 0.85 (0.74, 0.98) (Montgomery, Kamel, Saldana, Alavanja, & Sandler, 2008). Similarly, AHS study authors found no association between thyroid disease and glyphosate use in a cross-sectional analysis in the AHS; hyper-thyroidism: 0.98 (0.78., 1.2); hypo-throidism: 1.0 (0.91, 1.2); and, "other" thyroid disease: 0.97 (0.81, 1.2) (Goldner et al., 2010).

While these non-cancer health endpoints are wide ranging, in most instances only one study was available for a specific endpoint, therefore making it challenging to assess consistency in the

human population. Across these varied non-cancer, chronic health endpoints, there is little evidence of a role for glyphosate in the etiology of these non-cancer health effects.

b. 2. Cancer Effects

An effect estimate of the relation between glyphosate and other pesticide exposure and several different anatomical cancer sites is included in this literature review. Mainly performed within the AHS cohort, this literature review includes studies of prostate, lung, and colorectal cancer in addition to less common cancers in the human population such as pancreatic and stomach cancer in association with pesticide use. The role of pesticide use and lymphohematopoietic cancers and particularly non Hodgkin lymphoma (NHL) has been studied in several investigations external to the AHS cohort. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available; however, for NHL and other non-solid tumors, several investigations are published. In this section, we present a summary of the studies evaluating the carcinogenic potential of glyphosate and other pesticides in the human population.

b.2.1 Solid Tumor Cancer Studies (non-lymphohematopoietic (LHP) cancers)

Within the AHS study cohort, authors evaluated several anatomical cancer sites in relation to pesticide use. None of these investigations reported a significant statistical association with lifetime use of glyphosate specifically. While these are all initial, hypothesis-generating studies and require further follow-up studies to determine whether the true association with glyphosate is indeed null, the large sample size, extensive exposure data collection and validation, and comprehensive confounding variable adjustment in the AHS supports a conclusion of no association between glyphosate use and cancers studied at this time. In a cohort analysis of all glyphosate users, authors did not observe an association with all cancers combined (OR 1.0 (95% CI (0.90, 1.2)) or specific anatomical cancer sites, with the exception of a non-statistically significantly elevated risk of multiple myeloma based upon a small number of glyphosate exposed cases (De Roos, Blair, et al., 2005). A discussion of studies external to the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in section b.2.2 below.

Several AHS nested case-control analyses also provide information concerning the carcinogenic potential of glyphosate; there is no statistical evidence of an association with glyphosate presented across these investigations. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and breast cancer (OR 0.9 (95% CI (0.1, 1.1)) (Engel et al., 2005), colorectal cancer (OR 1.6 (95% CI (0.9, 2.9)) (W. J. Lee et al., 2007), lung cancer (no results shown due to lack of statistically significant risk estimate) (Alavanja et al., 2004), pancreatic cancer (OR (95% CI) 1.1 (0.6, 1.7)) (Andreotti et al., 2009), and prostate cancer (no results shown due to lack of statistically significant risk estimate) (Alavanja et al., 2003; Koutros et al., 2013), as well as cutaneous melanoma (no results shown due to lack of statistically significant risk estimate) (Dennis, Lynch, Sandler, & Alavanja, 2010). In a

population-based study external to the AHS, Canadian researchers reported non-significantly elevated odds of prostate cancer in relation to glyphosate use (OR 1.36 (95% CI 0.83, 2.25)) (Band et al., 2011). This study enrolled prostate cancer cases between1983-1990, prior to the PSA-era; therefore, the study includes more advanced tumors upon diagnosis, and is not comparable to Alavanja et al. (2003), which reflects cases during the PSA-era in which cases are typically identified at an earlier stage in the natural history of disease. Notably, in a prostate cancer follow-up study within the AHS, Koutros et al. (2013) did not identify an association with advanced prostate cancer (OR (95% CI) 0.93 (0.73, 1.18)) (Koutros et al., 2013). AHS investigators also examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with glyphosate use (maternal exposure to glyphosate: OR (95% CI) 0.61 (0.32, 1.16)); paternal exposure to glyphosate: OR (95% CI) 0.84 (0.35, 2.54)) (Flower et al., 2004).

Brain Tumors (Glioma): Population-Based Case Control Studies: External to the AHS cohort study, HED identified population-based case control studies which evaluated brain cancer in relation to pesticides use. Glioma is the most common type of brain tumor. In a study of ever-use of pesticides, authors identified 251 glioma cases between 1988 and 1993 in Nebraska, and controls (n=498) identified from the same region. Matching for age and vital-status, study authors reported a non-significant elevated odds of glioma (OR 1.5 (95% CI (0.7, 3.1)) in relation to glyphosate use; however the results were significantly different between those who self-reported pesticide use (OR 0.4 (95% CI (0.1, 1.6)), and for those whom a proxy respondent was used (3.1 (95% CI (1.2, 8.2)), indicating recall bias was likely a characteristic of this study (W. Lee et al., 2005). Three other population-based case control studies of glioma risk were part of this literature review; authors investigated the question among men and also among women participating in the Upper Midwest Health Study ((Carreon et al., 2005; Ruder et al., 2004; Yiin et al., 2012). Among glioma cases identified 1995-1997, authors found little evidence of a role of glyphosate in the etiology of this tumor. While herbicide use overall was non-statistically significantly linked to glioma in the study among men (OR 1.51 (95% CI (0.92, 2.48)), use of glyphosate was not linked to glioma among women (OR 0.7 (95% CI (0.4, 1.3). In the study by Carreon et al. (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to the study by Lee et al. (2005) noted above. Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (occupational use: OR 0.98 (95% CI 0.67, 1.43); home and garden use: OR 0.83 (95% CI 0.39, 1.73))(Yiin et al., 2012). Overall, this database presents little statistical evidence that there is a role for glyphosate in glioma risk in the Midwestern U.S.

Adenocarcinoma: Population-Based Case Control Study: In another population based case control study in the Midwest (NE), authors evaluated pesticide use and adenocarcinoma. Researchers did not observe an association between glyphosate exposure and either stomach

cancer (OR (95% CI) 0.8 (0.4, 1.5)) or esophageal cancer (OR (95% CI) 0.7 (0.3, 1.4)) (W. Lee et al., 2004). Exposure assessment was based upon self report pesticide use, with follow-up telephone interview to verify reported information. Cancer cases were identified through the state cancer registry, and confirmed by pathologist. While non-differential misclassification of either pesticide use could have occurred and attenuated or obscured results, it is unlikely there is a strong positive association with glyphosate and adenocarcinoma based the evidence presented in this study.

b.2.2 Non-Solid Tumor Sites (Lymphohematopoietic cancers)

There are several epidemiology studies of the possible link between pesticide use and lymphohematopoietic cancers; the study of NHL is particularly well represented in this small epidemiology database. All studies are case-control in design; there are no prospective cohort evaluations of this potential association. The presence of case control study design across this database limits development of firm causal inference.

Leukemia: In a population-based case control study in Iowa and Minnesota, authors investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR (95% CI) 0.9 (0.5, 1.6)) (Brown et al., 1990). The study population was identified from cancers reported to state registry or authorities in 1981-1984, and pesticide exposure assessment was performed through in-person interview which authors state likely reduced exposure misclassification (incorrect exposure information). The large sample size (578 cases and 1245 controls), exposure assessment methods, and confounding variable control are strengths of the study; however the lack of clear exposure-response information and the potential for recall bias are also present. In another population based case control study, cases were identified in 1987-1992 through the Swedish cancer registry. Authors reported a non statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR (95% CI) 3.1 (0.8, 12.0), controlling for age, gender, and residential location (Nordstrom, Hardell, Magnuson, Hagberg, & Rask-Andersen, 1998). However, these results are based on only 4 and 5 glyphosate exposed cases and controls, respectively, and should be interpreted with caution, as noted by the authors. At this time, the limited available literature concerning glyphosate use and leukemia cannot support a conclusion that glyphosate plays a role in leukemia.

Multiple Myeloma (MM): Using the same study population as noted above in reference to leukemia risk and pesticide use, Brown et al. (1993) studied whether pesticide use is also related to MM. Among men in Iowa (173 cases, 605 controls), authors observed a statistically non-significant elevated association with glyphosate use (OR (95% CI) 1.7 (0.80, 3.6))(Brown, Burmeister, Everett, & Blair, 1993). However, authors caution that while the study may lend support for the role of pesticides in general, the study limitations preclude use of evidence in support of any one compound. In the AHS cohort analysis by de Roos et al. (2005), researchers also reported a non-statistically significantly elevated risk of multiple myeloma among glyphosate users (OR 2.6 (95% CI (0.70, 9.4)), but this results was based upon only 32 MM

cases (20 of whom reported exposure to glyphosate), and authors did not observe evidence of an exposure-response trend by duration or intensity of pesticide use (De Roos, Blair, et al., 2005). Authors suggest there are too few cases of glyphosate exposed MM in the study to make a firm conclusion. In a population-based case control study in Canada, researchers reported non-statistically significantly elevated odds of MM in relation to glyphosate use (OR (95% CI) 1.22 (0.77, 1.93), based upon 32 and 133 glyphosate exposed MM case and controls, respectively (Pahwa et al., 2012). Within the AHS study population, molecular epidemiology researchers studied the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS); MGUS is considered a pre-clinical marker of MM progression. Authors did not observe a link with glyphosate use in the AHS cohort (OR 0.50 (95% CI (0.20, 1.0)) (Landgren et al., 2009). At this time, the epidemiologic database regarding the possible link between pesticide use and MM is too small and inconsistent to determine whether glyphosate plays a role in this cancer.

Lymphoma: The National Cancer Institute (NCI) performed a series of population-based case control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred NHL cases and controls, identified cases through disease registries which in many cases were histopathologically confirmed. Investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time. Early investigations (IA and MN) did not observe a link with ever-use of glyphosate (OR (95% CI) 1.0 (0.5, 2.2)); however authors did not adjust for exposure to other pesticides in this study (Cantor et al., 1992). Pooling data from several Midwestern states to increase study sample size (IA, MN, NE), and using additional pesticide use information to adjust the risk estimate (duration and frequency of use, telephone follow-up interview), Lee et al. (2004) observed a positive, non-significant association with glyphosate among those without asthma (OR (95% CI) 1.4 (0.98, 2.1)), adjusting for age, state and vital status (W. J. Lee, Cantor, Berzofsky, Zahm, & Blair, 2004). In a pooled analysis (n=3,417) of these same three study states, and utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, authors observed a similarly elevated, but non-statistically significant result: OR (95% CI) 1.6 (0.90, 2.8) (De Roos et al., 2003). These three evaluations reflect the same study population, use different levels of information (duration and frequency of exposure) and different analytic techniques (hierarchical regression and stratified analysis (by atopy)). While studies with increasing levels of refinement to method report a stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

Hardell et al. (1999 and 2002) performed two analyses of the possible link between pesticide use and NHL using the Swedish cancer registry and a telephone based exposure questionnaire to determine pesticide use. The initial investigation of 404 NHL cases and 741 control subjects included only 4 and 5 glyphosate exposed cases and controls, respectively. The risk estimate was elevated, but precision was low (OR (95% CI) 2.3 (0.40, 13.0)) (L Hardell & Eriksson, 1999). In

a pooled analysis reflecting the same study time period and prevalence of glyphosate use, Hardell et al. (2002) reported a non-statistically elevated odds of NHL among glyphosate users: OR (95% CI) 1.85 (0.55, 6.20)), however this estimate also lacks precision (L. Hardell, Eriksson, & Nordstrom, 2002). Authors stated glyphosate use was low in the time period of the study 1987-1990. Therefore, authors performed a new study in later time period (1999-2003) in which glyphosate use had increased. In this study, authors observed a similar risk estimate (OR (95% CI) 1.55 (0.77, 2.94)), among 910 NHL cases and 1016 non-NHL controls (Eriksson, Hardell, Carlberg, & Akerman, 2008). Authors conclude that the follow-up study, with a greater number of glyphosate exposed participants lends support to the conclusion glyphosate may play a role in NHL.

Within the Cross- Canada study of pesticides and health, authors estimated the association between glyphosate and NHL as well. These investigations reflect cases identified 1991-1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of cases, and implemented a two-tiered exposure questionnaire, and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the study results. Glyphosate was not among the primary findings of either study. The initial study within this population identified a non-statistically significant 20% increased risk of NHL (OR (95% CI) 1.20 (0.83, 1.74))(McDuffie et al., 2001), which attenuated in a follow-up study which controlled for exposure to other pesticides (OR (95% CI) 0.92 (0.54, 1.55)) (Hohenadel et al., 2011). Within this series of studies, authors also evaluated Hodgkin lymphoma (HL), and similarly observed little statistical evidence of an association, using similar study design and methods (OR (95% CI) 0.99 (0.62, 1.18)) (Karunanayake et al., 2012). In a separate study using a hospital-based case control study design (France (2000-04)), authors identified 491 NHL cases and 456 non-cases, and performed telephone-based questionnaire to assess pesticide and other confounding variables. Investigators did not observe an association between NHL and glyphosate use (OR (95% CI) 1.0 (0.50, 2.2)) (Orsi et al., 2009).

c. Glyphosate Summary

HED identified 55 environmental epidemiology studies regarding potential cancer and non-cancer, chronic health effects in association with pesticide use including glyphosate. As noted above, few of these studies reflected an *a priori* research interest in the potential role of glyphosate and chronic disease outcomes. Most studies were hypothesis-generating in nature, and study authors evaluated use of glyphosate in addition to several other pesticides. Therefore, the role of chance given the many different statistical tests performed and the lack of a pre-specified hypothesis limit epidemiologic inference. Given this and other limitations of these studies, we cannot conclude glyphosate plays a role in any of the health outcomes studied across this epidemiologic database. EPA will continue to follow the literature concerning the potential role of the chemical in respiratory health (asthma in particular), as well as adverse pregnancy and birth outcomes such as increased time to pregnancy. Across the several population-based case-control studies on NHL and pesticide use, some investigators observed non-statistically

significantly increased risk in relation to glyphosate use, while others reported no observation of a statistical association with glyphosate use. Variation in the quality of exposure assessment, study design and methods, as well as available information concerning potential confounding variables could explain these inconsistencies in the data. A prospective study devoid of the limitations of exposure recall inherent to case control studies will greatly aid causal inference. EPA will await with interest any new study using prospective exposure assessment methods to investigate the role of glyphosate and NHL and other lymphohematopoietic tumors.

5. CONCLUSIONS

The relatively high number of reported glyphosate incidents across the reviewed databases is likely a result of glyphosate being among the most widely used pesticides by volume. It should be noted that, most of the incidents reported are minor in severity meaning the symptoms were minimally traumatic and resolved rapidly.

HED found that the acute health effects reported to the incident databases queried are consistent with the previous incident report, and the other databases and medical literature reviewed. These health effects primarily include dermal, ocular, and respiratory effects. HED did not identify any aberrant effects outside of those anticipated. While inconvenient for those who suffer adverse health effects, effects are generally mild/minor to moderate and resolve rapidly.

The incident data available from IDS and NPIC suggest that homeowner mixing/loading/ applying (usually due to human errors and container leaks) are responsible for almost half of the reported incidents. SENSOR-Pesticides incident data are consistent with IDS and NPIC, also suggesting that application of glyphosate results in the most reported incidents (50%). However, the SENSOR-Pesticide incidents include both residential and occupational incidents. The incident data available from CA PISP suggests that occupational handling of equipment is responsible for most incidents due to equipment leaks and malfunction.

All of the databases showed occurrence of children's' exposures (ranging from 5% to 27% of the total). Based on the data in SENSOR, IDS, and NPIC, it appears that the childrens' exposures are due to postapplication exposure, accidental ingestion, and tampering with the product. Ocular exposure and symptoms were reported in all of the databases, to both occupational and nonoccupational users, as a result of splash to the face or touching their eyes with the product on their hands. These symptoms primarily included eye irritation, redness, burning and blurred vision.

Trends over time data from IDS (2008 to 2012), PISP (2005 to 2010), SENSOR-Pesticides (1998 to 2009) and AAPCC (2001 to 2012) data were reviewed. Based on IDS and AAPCC, which are primarily non-occupational cases, incidents appear to be decreasing over time. CA PISP data represents both occupational and non-occupational incidents. This data appears to be relatively

steady over time. The SENSOR-Pesticide data also represent both occupational and non-occupational cases. For this data, occupational case reports involving glyphosate appeared to be increasing until 2008 and non-occupational case reports appear to be increasing over time. The increase in non-occupational case reports may be reflective of increased SENSOR state capacity to collect non-occupational pesticide surveillance data.

Although animal studies showed glyphosate to have limited toxicity, medical case reports suggest that glyphosate end use products (formulated with different glyphosate salts and various concentrations of surfactants and adjuvants), may be more toxic than the active ingredient alone. Since human poisoning reviewed were not with the active ingredient (glyphosate) alone but with various mixtures, it is not easy to identify the exact cause. Nevertheless, the medical literature reviewed indicates that most of the accidental ingestions of glyphosate formulations resulted in mild symptoms such as irritation of oral and upper gastrointestinal mucosa and were self limited. However, intentional ingestions caused moderate to severe symptoms in multiple organs.

While HED identified several dozen glyphosate environmental epidemiology studies, few of these studies reflected an *a priori* research interest in the potential role of glyphosate and chronic disease outcomes, and most studies were hypothesis-generating in nature. Given this and other limitations of these studies, we cannot conclude glyphosate plays a role in any of the health outcomes studied across this epidemiologic database. EPA will continue to follow the literature concerning the potential role of the chemical in certain cancer and non-cancer outcomes. There were several (case control) studies evaluating the role of pesticide exposure including glyphosate and lymphohematopoietic cancers like NHL however limitations of study design and exposure assessment methods restrict the ability of these studies to inform causal inference. A prospective study devoid of the limitations of exposure recall inherent to case control studies could greatly clarify the current database. EPA will await with interest any new study using prospective exposure assessment methods to investigate the role of glyphosate and NHL and other lymphohematopoietic tumors.

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Appendix 1

Table A: Glyphosate Formulations Identified by the U.S. Forest Service (Diamond, 2011)

Formulation Name	Supplier	EPA Reg. No.	Form	Salt	%a.i.	Surfactant	Other
Accord	Monsanto	524-326	L	IPA	41.5%		Aq
Accord Concentrate	DowAgro Sciences	62719-324	L	IPA	53.8%		
Accord SP	DowAgro Sciences	62719-322	L	IPA	41%	X	No longer available
Accord XRT	DowAgro Sciences	62719-517	L	IPA	53.6%	X-[10]	
Accord XRT II	DowAgro Sciences	62719-556	L	DMA	50.2%	Inferred	
Aqua Star	Albaugh, Inc.	42750-59	L	IPA	53.8%	?[7]	
AquaMaster (a.k.a. Export and Rodeo)	Monsanto	524-343	L	IPA	53.8%		Aq
AquaNeat	Riverdale	228-365	L	IPA	53.8%		Aq
Buccaneer	Tenkoz Inc	55467-10	L	IPA	41.0%	X	
Buccaneer Plus	Tenkoz Inc	55467-9	L	IPA	41.0%	X	
Cornerstone	Winfield Solutions Agrisolutions	1381-191 71368-20-	L	IPA	41.0%	X	
Cornerstone Plus	Winfield Solutions	1381-192	L	IPA	41.0%	?	
Credit Extra	Nufarm	71368-65	L	Am K	17.86% 16.26%	X POEA?	
Credit Systemic Extra	Nufarm	71368-20	L	IPA	41.0%	X POEA?	
Diamondback	EZ-Ject	83220-1	Sh	IPA	83.5%		Injection
DuraMax	DowAgro Sciences	62719-556	L	DMA	50.2%	Inferred	
Durango (GF-1279)	DowAgro Sciences	62719-517	L	IPA	53.6%	X-[10]	
Durango DMA (GF-1280)	DowAgro Sciences	62719-556	L	DMA	50.2%	Inferred	
Eliminator [4,6]	Gro Tec, Inc	71995-27	L	IPA	41.0%	X	
Foresters' Non Selective	Riverdale	228-381	L	IPA	53.8%	None[8]	
Glyphogan	Makhteshim Agan	66222-105	L	IPA	41.0%	Inferred	
Glyphomax 41 Plus [4]	DowAgro Sciences	62719-322	L	IPA	41.0%	Inferred	
Glyphomax XRT	DowAgro Sciences	62719-517	L	IPA	53.6%	X-[10]	
Gly Star Plus	Albaugh Inc	42750-61	L	IPA	41.0%	X	
Glyphosate VMF	DuPont	352-609	L	IPA	53.8%		Cancelled ?
Glyphosate 41 Plus	CropSmart	42750-61-	L	IPA	41.0%	?	
GlyphoMate 41 or Pronto	PBI/Gordon Corporation	2217-847	L	IPA	41.0%	X	
Glyfos Aquatic	Cheminova A/S	4787-34	L	IPA	53.8%		Aq
Glyfos X-TRA	Cheminova A/S	4787-23	L	IPA	41.0%	X 15%[6]	
Glypro	DowAgro Sciences	62719-324	L	IPA	53.8%		
Gly-4 Plus	Universal Crop Protection Alliance	72693-1	L	IPA	41.0%	X	
Helosate Plus	Helm Agro US,	74530-4	L	IPA	41.0%	Inferred	

Formulation Name	Supplier	EPA Reg. No.	Form	Salt	%a.i.	Surfactant	Other
Hi-yield Killzall	Voluntary Purchasing	67760-49-7401		IPA	53.8%		Aq
Honcho (RoundupOriginal)	Monsanto	524-445	L	IPA	41.0%	X	
Honcho Plus	Monsanto	524-454	L	IPA	41.0%	X	
Imitator Plus	Drexel Chemical	19713-526	L	IPA	41.0%	?	
KGro Grass and Weed	Swiss Farms Pdts	71995-27-	L	IPA	1.92%		
Mirage	Loveland Products	34704-866	L	IPA	41.0%	Inferred	
Ranger Pro	Monsanto	524-517	L	IPA	41.0%	X	
RapidFire	DowAgro Sciences	62719-556	L	DMA	50.2%	Inferred	
Rattler	Monsanto	524-445-ZE-	L	IPA	41.0%		
Razor	Nufarm	228-366 [1]	L	IPA	41.0%	X 8%[8]	
Razor Pro	Nufarm	228-366 [1]	L	IPA	41.0%	X 14%[8]	
Rodeo	DowAgro Sciences	62719-324	L	IPA	53.8%		
Roundup Original Max	Monsanto	524-539 [3]	L	K	48.7%	X	
Roundup Pro	Monsanto	524-475 [2]	L	IPA	41.0%	X 14.5%	
Roundup Pro Concen.	Monsanto	524-539 [3]	L	IPA	50.2%	X 13%	
	Monsanto	524-505	G	Am	71.4%	X	
Roundup ProMax	Monsanto	524-579	L	K	48.7%	X	
Roundup UltraMax	Monsanto	524-512	L	IPA	50.2%	X	
Roundup UltraDry	Monsanto	524-504	G	Am	71.4%	X 25%	
Roundup WeatherMax	Monsanto	524-537	L	K	48.8%	X	
RT 3	Monsanto	524-544	L	K	48.8%	X	

[1] Razor and Razor Pro appear to have the same EPA Registration number but the formulations are different.

[2] Based on the EPA master product label, this registration number applies to the following brand names: Roundup Ultra Herbicide; Roundup Ultra RT Herbicide; Roundup Pro Herbicide; Roundup Original II CA; MON 77360 Herbicide; Roundup W Herbicide; Gly 41 Herbicide.

[3] Based on the Product Labels and MSDSs, Roundup Original Max and Roundup Pro Concentrate have the same EPA registration number but contains different salts of glyphosate.

[4] Need specimen label. The EPA labels are not clear (are ambiguous) in terms of the formulation(s) covered.

[5] MSDS cannot be located, including searches of http://www.msdsonline.com and http://www.cdms.net.

[6] From Lajmanovich et al. 2003 but not specifically identified as Glyphos Plus.

[7] Bringolf et al. (2007) state that Aqua Star does not contain the MON 0808 POEA surfactant. It is not clear whether or not this formulation contains a less toxic surfactant.

[8] Information confirmed by Nufarm (Ehresman 2010a).

[9] Dow (Fonseca 2010a) has indicated that Accord SP (EPA Reg. No. 62719-322) is not longer commercialized.

[10] Based on information provided by Dow AgroSciences (Fonseca 2010a)

Key:

Form: L=Liquid; G=Granular; Sh=Shells.

Salt: Am=Ammonium salt: DMA=Dimethylamine salt; IPA=Isopropylamine salt; K=Potassium salt;

Other: Aq=Aquatic application; Inj=Injection.

Formulations containing herbicides other than glyphosate as the a.e. are not included.

Table B: Summary of References for the Medical Literature Search		
Study	**Author**	**Summary**
1. Rosen's Emergency Medicine: Concepts and Clinical Practice. 6th ed.	Aaron CK. (2006)	Glyphosate inhibits the enzyme 5-enolpyruvyl-shikimic-3-phosphate-synthase in plants; however, mammals do not have this enzyme.
2. Annual Report	American Association of Poison Control Centers (2011)	According to the American Association of Poison Control data in 2011, glyphosate ranked first with 3,570 exposures among reported human exposures to herbicides (total of 8377); 90% were unintentional.
3. Skin Toxicity from Glyphosate-Surfactant Formulation	Amerio P., Motta A.et al. (2004)	A 78 year old woman presented with extensive chemical burns on her back, knees and legs caused by accidental contact with a glyphosate-surfactant formulation. Sheets of necrotic epidermis had sloughed, leaving extensive erosions. Bullae were present on the dorsum of the feet.
4. Glyphosate poisoning.	Bradberry SM. (2004)	The mechanisms of toxicity of glyphosate formulations are complicated. Not only is glyphosate used as five different salts but commercial formulations of it contain surfactants, which vary in nature and concentration. Ingestion of >85 mL of the concentrated formulation is likely to cause significant toxicity in adults.
5. Extreme hyperkalemia in a patient with a new glyphosate potassium herbicide poisoning: report of a case.	Bando H., Murao Y, (2010)	Ingestion of Roundup Maxload which contains high concentration of glyphosate potassium can cause extreme hyperkalemia with cardiac toxicity and metabolic acidosis.
6. Clinical impact of upper gastrointestinal tract injuries in glyphosate-surfactant oral intoxication.	Chang C.Y., (1999)	Authors studied lesions in gastrointestinal tract of 50 patients with glyphosate-surfactant oral ingestion as a suicide attempt. They found that esophageal injury was seen in 68% of the patients; gastric injury in 72%, and duodenal injury in 16%.
7. Refractory cardiopulmonary failure after glyphosate surfactant intoxication: a case report.	Chang CB, Chang CC (2009)	Patient ingested about 400 mL of concentrated glyphosate developed shock, respiratory failure, hyperkalemia, and acidosis. In spite of comprehensive supportive treatment, patient died 3 days after admission.
8.The epidemiology of glyphosate-surfactant herbicide poisoning in Taiwan, 1986-2007: a poison center study.	Chen YJ, Wu ML, Deng JF, Yang CC (2009)	A retrospective analysis of all GlySH exposures reported to the Taiwan National Poison Control Center between 1986 and 2007. Irritation of the oral mucous membrane and gastrointestinal tract was the most frequently reported effect. Other effects recorded were pulmonary dysfunction, oliguria, metabolic acidosis, hypotension, leukocytosis and fever. Cardiovascular collapse and respiratory failure were two major cause of fatality (Y. J. Chen, Wu, Deng, & Yang, 2009).
9. Glyphosate Human Health and Ecological Risk Assessment (USDA)	Durkin PR (2011)	Authors mentioned that there were various concentrations of POEA surfactant, glyphosate salts and other ingredients in different glyphosate products and the resulting adverse health effects may be different.
10. Handbook of Pesticide Toxicology, 2nd edition (Inhibitors of Aromatic Acid Biosynthesis).	Farmer D., (2001)	Glyphosate contains a carbon and phosphorous moiety but it is not a cholinesterase inhibitor and does not affect the nervous system in the same way as organophosphate insecticides
11. Pesticide-Associated Pemphigus Vulgaris	Fisher KR., et al., (2008)	Described a patient who developed pemphigus vulgaris (PV) on his body and extremities, after an occupational exposure to fumes of burning empty glyphosate drums. PV is an autoimmune skin lesions characterized by bullae that rupture quickly and progress to crusted erosions.
12. **Determination of the herbicide glyphosate and its metabolite in**	Hori, Y.	Authors described the method for determining glyphosate and its metabolites by GC-MS.

biological specimens by gas chromatography-mass spectrometry. A case of poisoning by roundup herbicide		
13. Herbicide roundup intoxication: successful treatment with continuous renal replacement therapy.	Hour BT., Belen C., Zar T., Lien YH., (2012)	Roundup toxicity is mainly due to surfactant, which interferes with the mitochondrial wall, destroying the proton gradient required for energy production. Patient develops cardiogenic shock, lactic acidosis and multiorgan failure. Early administration of hemodialysis would be the treatment of choice (Hour, Belen, Zar, & Lien, 2012).
14. Erythema multiforme like eruption due to an irritant contact dermatitis	**Heras-Mendaza F., et al. (2008)**	A 37-year –old female was exposed to glyphosate herbicide (Touchdown Premium) when the backpack containing the herbicide broke and wet her clothing. She suffered from the irritant contact dermatitis, followed by erythemato-purpuric plaques developed on the upper extremities, on the abdomen, axilla and groin.
15. Glyphosate-surfactant herbicide products containing glyphosate potassium salt can cause fatal hyperkalemia if ingested in massive amounts.	Kamijo Y, Mekari M, (2012)	A 69-year old female ingested about 500 mL of Roundup Maxload contains 48% glyphosate potassium developed severe hyperkalemia and refractory ventricular tachycardia. It was considered that hyperkalemia was caused by Roundup Maxload which contains potassium 2.6 mEq/mL. Endoscopy showed pharyngeal edema, esophageal and gastric erosions.
16. Early continuous dialysis in acute glyphosate-surfactant poisoning.	Knežević V. (2012)	A 36-year old male took about 300 ml of glyphosate-surfactant, six hours later he developed hypotension, oliguria and renal failure. Hemodialysis brought the complete recovery of renal function on the 5th day (Knezevic et al., 2012).
17. Clinical presentations and prognostic factors of a glyphosate-surfactant herbicide intoxication	Lee H.L., Chen K.W., Chi C.H., Huang J.J., Tsai L.M., (2000)	Retrospective review of 131 cases in Taiwan University hospital. The most common symptoms included sore throat (79.5%), and nausea with or without vomiting (73.8%). The most common laboratory findings were leucocytosis (68.0%), low serum bicarbonate (48.1%), and acidosis (35.8%).
18. The early prognostic factors of glyphosate-surfactant intoxication.	Lee C-H, Shih CP, Hsu KH, Hung DZ, Lin CC. (2008)	GlySH poisoning is multiorgan toxicity. Metabolic acidosis, hyperkalemia, respiratory distress needing intubation, tachycardia, and elevated serum creatinine level are useful prognostic factors for predicting GlySH mortality.
19. Severe adverse effects related to dermal exposure to a glyphosate-surfactant herbicide	Mariager TP., Madsen PV ., (2013)	A 43-year old man diluted the glyphosate-surfactant herbicide with water and shook the bottle; the contents accidentally sprayed on him. He did not wash the exposed areas. The next day he developed local swelling, bullae and exuding wounds on right hand, arm, upper arm and axilla regions. Soon it changed into second degree skin necrosis with detachment of the epidermis. In addition he had touched his face with contaminated hands resulting in a peri-orbital edema. Nerve conduction study (NCS) showed reduced nerve conduction in distal axons on the medial, ulnar and radial nerves. Imaging revealed edema of the soft tissue and osteopenia of carpal bones.
20. Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity.	Mesnage R, Bernay B, Séralini GE. (2012)	All formulations are more toxic than glyphosate. Polyethoxylated tallowamine POE-15 appears to be the most toxic principle against human cells (cell membrane disruption and necrosis). Since pesticides are always used with adjuvants that could change their toxicity, it is necessary to assess the toxicity of whole formulations in addition to the active ingredient (Mesnage, Bernay, & Seralini, 2013).
21. Glyphosate–surfactant herbicide-induced reversible encephalopathy.	Malhotra R.C., Ghia DK.(2010)	A 71-year-old male who attempted suicide with GlySH developed a prolonged (clinically unresponsive for more than 7 days, demonstrated with electroencephalogram) but reversible encephalopathy suggestive of the acute central nervous system (CNS) toxicity of the product.

22. Glyphosate based pesticides affect cell cycle regulation.	Marc J. et al., (2004)	Glyphosate based pesticide products disrupt cell-cycle control mechanisms, which may be relevant for cancer as well as noncancer health outcomes.
23. Comparative effects of the Roundup and glyphosate on mitochondrial oxidative phosphorylation.	Peixoto F (2005).	The potential toxicity of the herbicide Roundup and its fundamental substance (glyphosate) was tested in isolated rat liver mitochondria. Roundup interferes electron transfer (by partially inhibiting mitochondrial complexes II and III) and depresses ATPase activity, while glyphosate used in the same concentrations does not induce any significant effect.
24. Acute glyphosate-surfactant poisoning with neurological sequels and fatal outcome	Potrebić O, Jović-Stosić J, (2009)	A 56 year old woman ingested about 500 mL of herbicide containing glyphosate isopropylamine salt developed hypotension, hyperkalemia, respiratory and renal failure, coma and had a lethal outcome. MRI revealed bilateral extensive white matter lesions of the brain stem and Pons.
25. Herbicide (Roundup) pneumonitis.	Pushnoy LA, Avnon LS, Care RS (1998).	A 42-year old worker had inhaled Roundup while cleaning the spraying device in a confined space. He developed shortness of breath, irritative cough, dizziness and hemoptysis. Otolaryngology evaluation showed signs of burns in the mucosal membranes of the pharynx and larynx. Chest X-ray showed acute massive pneumonitis.
26. Dysphonia following glyphosate exposition	Ptok M (2009)	A 26-year-old teacher who used glyphosate formulation correctly but suffered from severe dysphonia after few hours. Laryngoscopy revealed decreased vocal fold mobility suggesting innervation impairment. The symptoms resolved spontaneously 6 weeks later and vocal fold mobility returned to normal.
27. A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning	Roberts DM. et al (2010)	601 cases of intentional ingestion between 2002- 2007 in two hospitals in Sri Lank were followed. 86% of patients had mild symptoms and signs such as nausea, vomiting, diarrhea, abdominal pain, transient hypotension, and tachypnea (respiratory rate >25/minute). 5.5% of patients were in moderate to severe condition with depressed level of consciousness, had respiratory failure and severe hypotension (mean arterial blood pressure <70 mmHg). 3.2% of cases were fatal (median time to death was 20 hours). Glyphosate plasma concentration >734 μg/mL was the best predictor of fatality. Glyphosate product was rapidly absorbed from the GI tract, followed first-order elimination with a half-life ranged from (2.7-3.6) hours.
28. Pathological and toxicological findings in glyphosate-surfactant herbicide fatality: a case report.	Sribanditmongkol P, Jutavijittum P, (2012)	A 37-year-old woman intentionally ingested approximately 500 mL of concentrated Roundup formulation (41% glyphosate as the isopropylamine salt and 15% polyoxyethylene amine). The postmortem examination revealed hemorrhagic areas in the gastric mucosa of anterior fundus and the small intestines had marked dilatation and thin walls. The glyphosate levels of serum and gastric content were 3.05 and 59.72 mg/mL, respectively.
29. Aseptic meningitis in association with glyphosate-surfactant herbicide poisoning.	Sato C, et al (2011)	Patient demonstrated Kernig's sign and significant neck stiffness with rigidity of the extremities as well as consciousness disturbance and fever (38.4°C). Investigations of cerebrospinal fluid (CSF) revealed the presence of glyphosate (122.5 μg/mL), significant elevation of IL-6 (394 μg/mL), and pleocytosis (32 cells/μL) with monocyte dominance. All bacteriological and virological tests were negative.
30. Glyphosate herbicide formulation: A potentially lethal ingestion.	Stella J, Ryan M. (2004)	Although glyphosate is generally regarded as minimally toxic, severe poisoning with glyphosate formulation may be refractory even to the most intensive supportive care. The triad of pulmonary edema, metabolic acidosis and hyperkalemia indicates poor outcome. Polyethoxylated tallowamine (POEA) toxicity can cause gastric pain, pulmonary edema, impaired consciousness and hemolysis. Glyphosate alone can

		also cause gastrointestinal erosions, renal toxicity, metabolic acidosis and central nervous system effects.
31. Roundup intoxication and a rationale for treatment.	Sampogna R.V., Cunard R. (2007)	Patient developed acute renal failure with oliguria after ingestion of Roundup. His condition improved rapidly and renal function returned to normal with hemodialysis treatment (Sampogna & Cunard, 2007).
32. Rapid lethal intoxication caused by the herbicide glyphosate-trimesium (Touchdown).	Sorensen FW, Gregersen M., (1999)	A 6-year-old boy who accidentally ingested a mouthful of glyphosate-trimesium died within few hours. The same happened to a 34-year-old woman who intentionally ingested approximately 150 ml of glyphosate-trimesium. The speed of which death occurs is much more rapid than lethal intoxications with glyphosate (isopropylamine salt), also known as 'Roundup'.
33. Acute Poisoning with a Glyphosate-Surfactant Herbicide ('Roundup'): A Review of 93 Cases	Talbot (1991)	The average amount of the 41% solution of glyphosate surfactant herbicide ingested by lethal cases was 184 ± 70 ml (range 85-200 ml). There were erosion of gastrointestinal tract, pulmonary, renal and central nervous system dysfunction. Deaths followed refractory hypotension or pulmonary edema.
34. Glyphosate Induced Severe Tubulointerstitial Nephritis Requiring Hemodialysis.	Yoo SH, Kim BS, Lee HY., (2010)	Reported the first case of glyphosate induced severe tubulointerstitial nephritis (not secondary to cardiovascular collapse) requiring hemodialysis. Kidney biopsy revealed drug-induced nephrotoxic injury. Patient had ingested about 90 mL of the product.
35. Parkinsonism after chronic occupational exposure to glyphosate	Wang G., Fan X-N., (2011)	A 44 year old woman who worked exclusively at the glyphosate production division for 3 years, 50 hours each week, wearing only basic PPE (gloves or face mask) was diagnosed with Parkinsonism syndrome. She had weakness, dizziness, and blurred vision. She also had a resting tremor, global akinesia and rigidity in all four limbs. MRI revealed bilateral hypotense lesions in the globus pallidus, the substantia nigra and in the cerebral peduncle.
36. Determination of glyphosate in heart blood of corpse by ion chromatography.	Wang Y., et al., (2012)	Ion chromatography is a simple, sensitive and accurate method to prove that the patient had a glyphosate poisoning.
37. Rhabdomyolysis from an intramuscular injection of glyphosate-surfactant herbicide.	Weng SF, Hung DZ, Hu SY, Tsan YT, Wang LM (2008)	Authors described the Rhabdomyolysis (destruction of muscle cells) in the upper limb due to intramuscular injection with the glyphosate product in a suicide attempt (Weng, Hung, Hu, Tsan, & Wang, 2008).
38. Determination of glyphosate and AMPA in blood and urine from humans: About 13 cases of acute intoxication.	Zouaoui K, Dulaurent S, Gaulier JM, Moesch C, Lachâtre G. (2013)	In mild to moderate intoxications blood glyphosate concentrations had a mean value of 61mg/L (range 0.6-150mg/L), in severe intoxication cases, the blood glyphosate concentrations were around 838mg/L and in fatal cases 4146mg/L (range 690-7480mg/L).

Appendix 2

Human Incidents	Chemical: Glyphosate	PC Code: 103601, 103603, 103604, 103605, 103607, 103608, 103613, and 417300

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
019417 - 00001	1/1/2008	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	A 74 year old male ingested 1/2 gallon of Roundup Concentrate. He experienced vomiting, diarrhea and high blood pressure
019542 - 00001	1/1/2008	CA	071995-00032	ROUNDUP WEED AND GRASS KILLER READY TO USE PLUS	103601	MODERATE	The caller states that she is a medical doctor calling on behalf of her friend who has been suffering from Roundup poisoning for years. The caller states that her friend self diagnosed the Roundup poisoning. The woman is being treated for chronic fatigue syndrome and was prescribed to give herself heparin weekly for the condition. She was giving herself heparin that was manufactured in China and it had a hyper sulfur content. She is the only person of her MD's patients who reacted adversely to the heparin getting skin pain and flushing. The patient also has history of asthma but is not compliant with any therapies for the asthma. The caller is not treating the woman. PCC confirmed the exposure was when the gardener sprayed the product outside her home.
019726 - 00001	3/1/2008	HI	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Man was working with Roundup Herbicide unknown formulation about four weeks ago. He does not have the container to confirm the product ingredients. He stated while mixing the product he got some on his hands. He did not wash with soap and water until a few hours passed. The next day his hands were a reddish brown then light redness and the skin sloughed off. His hands are now discolored and sensitive. He has not seen a doctor. At the end of the conversation, he mentioned he is a chemist and works with chemicals. He usually does not get anything on his hands as he wears protective gloves.
019727 - 00001	6/3/2008	CA	000524-00475	ROUNDUP PRO	103601	MODERATE	A worker got overspray from Roundup PRO in his eyes about 1 0 days ago. He rinsed his eyes on the sight and has been to the eye doctor. He has been prescribed eye drops for the last 10 days but his eyes are red and still irritated. He is worried about

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							long term damage to his eyes or if there is something else he should be doing. Follow up indicated that one of the problems with eye drops is an allergic reaction to the drops. There are also some nasal symptoms, so an allergy to the eye drops is likely. He went to MD who advised him to stop using the drops.
019740 - 00001	5/7/2008	SILER CITY, NC	004787-00023	GLYFOS X-TRA	103601	MODERATE	A 36 year old male reports product was sprayed in his face and nose due to the fact that he claimed his sprayer was not attached correctly. There was no skin irritation; however, he reportedly started getting a cough, nasal discharge and a fever the next day. After examination by a doctor, caller reports symptoms were due to pneumonia. He was given antibiotics.
019741 - 00001	6/24/2008	NC	004787-00023	GLYFOS X-TRA	103601	MODERATE	A 51 year old male had product blown back on him by wind as he applied it. The product got primarily his face, head, arms and legs. Approximately 12 hours later, this man reportedly had a blotchy rash all over his head, arms, back, legs and chest with welts on his back and side. After an examination by a doctor, caller states husband was diagnosed with poison oak.
019746 - 00001	5/7/2008	HEATH, OH	004787-00023	ACE READY-TO-USE WEED & GRASS KILLER 2	103601	MODERATE	A 73 year old female reportedly got some product on her shoes. After wearing these same shoes the following Monday, caller noticed her feet were red and burning. Following soaking her feet in apple cider vinegar, caller claimed the skin on her feet was peeling off. Medical treatment was sought and caller was prescribed topical medication. Approximately three and 1/2 weeks later, caller reported having medical evaluation done and symptoms were resolving.
019772 - 00004	5/19/2008	READING, PA	062719-00322	GLYPRO PLUS HERBICIDE	103601	MODERATE	A 28 year old female states that on Tuesday she was spraying the dilute product and when she finished she removed the top of the sprayer and was hit "across her eyes" with the mist of the product. She didn't feel anything go into her eyes nor did she feel any discomfort at the time. She

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							states that last night while doing some trimming with her 'weed whacker' she got some grass in her eye. She couldn't get it out and so she went to the MD who rinsed her eye and gave her antibiotic eye drops. She is now wondering if the product could have also been involved with the irritation. She was asymptomatic before getting the grass in her eye.
019803 - 00001	6/11/2008	HI	034704-00890	KLEENUP PRO HERBICIDE	103601	MODERATE	An adult female was using product at her workplace. The product was mixed 2.5oz per gallon of water. The hose kept coming off and the diluted product saturated her gloves and pants. It was about 1 hour before she could rinse her skin. The next day she experienced decreased urine output, headache and nausea. Her headache and nausea resolved in 24 hrs. She went to MD to address her decreased urination and was diagnosed with a UTI. She was placed on antibiotic and her symptoms resolved.
019862 - 00002	5/7/2008	PA	071995-00032	ROUNDUP WEED AND GRASS KILLER READY TO USE	103601	MODERATE	Caller states that she was using Roundup Ready to Use yesterday morning for about 30 minutes and there was no noted exposure to the product except that she felt like she was breathing it in. She began to have symptoms of vomiting, bloody diarrhea.
019862 - 00007	5/27/2008	CA	071995-00023	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	103601	MODERATE	Caller states his spouse used a Roundup Ready to Use formulation one year ago. Some of the Roundup got onto her hands during the spraying. She did not wash her hands for several hours, until after the project was completed. No skin irritation or rash reported at the time of the exposure or near post-exposure. Husband calling the MRPC to see if the product is absorbed through the skin. His spouse has been diagnosed with squamous cell cancer. He wonders if this could be related to the use of Roundup with dermal exposure.
019862 - 00008	5/27/2008	IL	071995-00023	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	103601	MODERATE	Grandmother calling about her 5 year old granddaughter who, along with some friends, used a gallon of Roundup Weed and Grass Killer Ready to Use. They used the entire bottle on the weeds. There may have been some dermal exposure, but the children were bathed that day. There were no

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							complaints of a sore throat or nasal symptoms on the day of the exposure. The 5 year old female developed a cough and fever was diagnosed with pneumonia four days later. She is going to see a pulmonologist in one month. The caller would like to know if the child is poisoned. Caller states to her knowledge, none of the other children have been sick.
019862 - 00009	5/10/2008	IA	000524-00343	AQUAMASTER	103601	MODERATE	Mother calling about 24 year old son that was pulling out cattails by hand about 5-7days post herbicide treatment with Aquamaster mixed per direction with a nonionic surfactant. Unknown if he was wearing gloves at the time, but he did have on waders. Exposure was greater than six months ago. Since that time he has complained of sneezing, coughing, nasal drainage, gastrointestinal upset and headache. Man has been evaluated by PMD to rule out gastric reflux. He was also evaluated by ENT physician. Mother is calling today as she and son have noted a similar odor of product on son's breath recently. Man denies any oral exposure and questions inhalation of substance during time of dermal exposure. No recent contact with product.
019862 - 00010	5/15/2008	IN	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	Caller states that several years ago (2-3 years), she used a Roundup product or another herbicide to kill some poison ivy. She recalls that she mixed the product in a bucket, and some of the product may have splashed onto her leg(s). She developed a rash on her leg shortly after this exposure that she assumed was poison ivy. Then, she experienced tingling down her leg that she cannot get rid of. Her doctor told her that she had nerve damage. She had a hip and knee replaced and thought that may help the symptoms, but it didn't. Caller has accepted that there is nerve damage, but she is wondering if it could be due to this possible exposure.
019862 - 00012	6/2/2008	MN	071995-00032	ROUNDUP WEED & GRASS KILLER READY TO USE	103601	MODERATE	Caller states her 5 year old has had a reoccurring spider like rash on areas of his skin for about 1 month. Mother notices the rash after he has been

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							playing outside. The mother is worried that it could be due to the Roundup Weed and Grass Killer Ready To Use that her husband sprayed weeks ago. Her son was not around the area when it was sprayed or while it was still wet. The rash comes and goes and does not bother her son. No itching noted.
019862 - 00013	6/10/2008	MO	071995-00032	ROUNDUP WEED & GRASS KILLER READY TO USE	103601	MODERATE	An emergency department physician was calling, about a 68 year old male that presents with a history of sudden onset nausea and ataxia. No vomiting noted. The man stated that he had been spraying weeds with Roundup earlier today but does not think he got any of the product on his skin. The physician states she will be admitting the man for further workup to try and determine the cause of the symptoms.
019862 - 00015	6/8/2008	GA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he applied an unknown formulation of Roundup about a month or so ago while wearing gloves but short sleeves. It may have been windy, and the back spray may have gotten onto the exposed areas of his arms. Caller noticed red blotches from his wrists to his elbows shortly after applying the Roundup. The areas are not raised and they do not itch or hurt. He never recalls his arms being wet with the Roundup. He has been applying Cortisone 10 to both arms with no improvement. Caller has an appointment for MD to look at his arms tomorrow.
019862 - 00016	6/15/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he sprayed Roundup Concentrate (unknown exact formulation) that was diluted 3 ounces to 1 gallon of water. A day or two later he pulled up the grass that he had sprayed. Immediately afterwards, he developed blotches and hives on his arms and trunk. He has been to the emergency room twice for treatment of hives and pruritis. He was given prednisone 10 mg the first time and hydroxyzine the second time. The emergency room didn't believe that his signs and symptoms were related to the Roundup, but rather that he was having an allergic reaction to something.

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019862 - 00017	6/21/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Physician Assistant calling about a 38 year old female that came to the Emergency Department with complaints of malaise, weakness and appeared in poor health. She is jaundiced with acute onset hepatitis. Symptoms started four days earlier. The woman was working in her yard and mixed an unknown Roundup product and an Ortho Weed B Gone product together with her hands. She washed her hands later after she worked in the yard. The woman has associated her illness with this exposure. The attending MD and Physician Assistant do not think either product has anything to do with the woman's illness, but they wanted to double check possible toxicity. The woman is going to be admitted to the ICU.
019877 - 00001	6/1/2008	SHARPSBURG, GA		ROUND-UP 1.33 GALLON WEED KILLER WITH "PULL 'N SPRAY" FEATURE	103601	Unknown or No Effects	A 45 year old male was sprayed directly in the face with product. He was using a 1.33 Gallon container of Round-Up weed killer with a "Pull 'N Spray" delivery system, the pull handle snapped off with the contents under pressure. He got the product in his eyes, nose, and mouth. He does not feel that this product delivery system which is built into the packaging is safe and he believes that it should be considered for recall.
019910 - 00433	5/20/2008	PENNS GROVE, NJ	071995-00008-000239	TOTAL KILL WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller used this product to treat ivy in his yard. Two weeks later his 5 year old son had a seizure for the first time.
019952 - 00001	6/25/2008	IN	034704-00890	MAKAZE	103601	MODERATE	An adult male used the product and thought he may have ingested some of the product through the spray about 3-4 weeks ago. Caller said the product was diluted when he was using it. He has been seeing a MD because he has a heavy spot on his chest like a cough that never goes away. He had an X-ray done and everything was normal.
019978 - 00466	7/22/2008	CA	071995-00008-000239	TOTAL KILL WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	An adult female used the product on the sidewalk. It was windy day and some product got on her arms and legs. Her right hand and leg were in contact with the product. Caller wiped the area with a dry paper towel and did not shower until the

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							next morning. Three days later she broke out in a light fine rash on both her arms and legs. She went to the MD who diagnosed it as an allergic reaction.
020042 - 00001	7/1/2008	IL	071995-00008	ROUNDUP READY-TO-USE WEED & GRASS KILLER	103601	MODERATE	Caller states she inadvertently sprayed Roundup Weed and Grass Killer RTU in her eye and then rinsed for about 5 minutes. She went to the ED for evaluation. She was diagnosed with an abrasion to the right eye and given an analgesic and antibiotic. She had an appt to follow up with her optometrist. The caller was not sure if the pressure from the spray caused the injury or if the sprayer hit her in the eye or just the Roundup.
020043 - 00001	7/1/2008	NY	071995-00020	ROUNDUP CONCENTRATE POISON IVY AND TOUGH BRUSH KILLER 1	103601	MODERATE	Wife calling about her husband who used Roundup Poison Ivy and Tough Brush Killer1 Concentrate that was diluted per label instructions. He also used an Ortho product around the same time. The man showered afterward. He started to feel sick that evening, and was worse the next day with chills, sweating and weakness. He was admitted to the hospital for treatment of pneumonia. The man was very dehydrated on admission. He complained of a severe headache and stomach pains. He had a CT scan of his lungs. Four days later, the physician called from the hospital to state that the man was admitted to the hospital for treatment of pneumonia.
020044 - 00001	7/1/2008	IA	071995-00017	ROUNDUP CONCENTRATE WEED & GRASS KILLER	103601	MODERATE	A 55 year old male was calling about his ongoing occupational dermal and inhalational exposure to Roundup Weed and Grass Killer Concentrate for three months. He complains of vertigo.
020048 - 00001	6/1/2008	MN	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	About one month ago a 52 year old female stated while outside treating weeds with an unspecified Roundup product, her hand had turned brown in color immediately after a dermal exposure to the product.
020065 - 00007	6/30/2008	HOT SPRINGS, AR	062719-00517	ACCORD XRT	103601	MODERATE	Caller is a company rep calling for an MD that is treating a patient that was using these three products in conjunction around 24 hour ago. Caller is not certain about the details of the exposure. Pt. was presenting with SOB and other symptoms, which the caller is unsure of. MD is inquiring

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							about the products. Pt. is currently being treated. Two days later, the patient's symptoms had resolved and he was back at work. It is unclear what the doctor's assessment revealed.
020083 - 00001	8/6/2008	CA	071995-00023	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	103601	MODERATE	Caller states a Roundup Ready to Use product was sprayed in his face and eyes while he was trying to adjust a clogged hose on the spray container. Man rinsed his eyes with water but did not elaborate on the method used. He complains that his left eye is still burning and the vision is blurred. On follow up, the man did rinse his eyes with water a little longer and then went to see his doctor who checked his eye and noted a small burn on the corneal surface. He was prescribed an ointment to use but he does not know its name. The doctor will follow up with him in 4-5 days.
020085 - 00001	7/1/2008	FL	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller states that about a month ago she was weeding with her sister and her sister was spraying Round Up Ready to Use. The caller began to have a burning sensation to her eye and at the time she was not sure if it was sweat in her eye or Round Up. She did go inside and wash off her face and then place a warm compress to her eye. No irrigation done at the time. The caller has been dealing with eye issues since that time. The caller reports that her eyes are red and tearing constantly. She first went to her PMD who prescribed antibiotic eye drops. Those drops did not work and she went to an ophthalmologist who prescribed prednisone for her eyes. That did not work and she has seen an allergist who prescribed eye drops which have also not resolved her symptoms.
020087 - 00001	6/1/2008	IL	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	
020089 - 00001	8/22/2008	MO	071995-00007-059144	ELIMINATOR W & G KILLER SUPER CONCENTRATE	103601	MODERATE	Caller states her yard was sprayed with diluted Eliminator Super Concentrate on Friday morning. Later that day, her child was playing out in yard and could have accessed the area sprayed but it is not confirmed. The child became delusional and

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							hallucinated 30 minutes after playing outside. She was evaluated in the emergency department where a CT scan was done. Drug screens were all negative.
020090 - 00001	7/1/2008	OK	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states the rock area around her flowerbeds was sprayed with Roundup by lawn workers about 1.5 months ago. About an hour after spraying she walked on the rocks to access her hose while wearing socks and tennis shoes. When she turned on the hose, her feet got wet from the water. Worked in the yard for about an hour and then showered with soap and water. About 2 days later her foot broke out into a rash. The urgent care told her it was a topic dermatitis or eczema and a steroid cream was prescribed and used. She followed up with her PMD who referred her to the dermatologist because her symptoms were worsening. The dermatologist scraped the area and diagnosed her with a fungus infection.
020091 - 00001	7/1/2008	MO	000524-00475	GLY-41 HERBICIDE	103601	MODERATE	Caller states that about a month ago he had his arms emerged into a sprayer tank with the diluted Gly-41 product to unclog the sprayer. He did wash up immediately after the exposure but he began to have diarrhea soon after the exposure and he is still having it (symptoms persisting one month).
020092 - 00001	8/1/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Woman calling that was spraying unknown formulation of Roundup Herbicide Concentrate when the sprayer cap came off and sprayed her in the face and eyes. She took a shower and rinsed her eyes for about 30 minutes as they were stinging and burning. She is still having a burning sensation and hazy vision at the time of the call. The eye is not tearing. The next morning, the woman states she had rinsed her eye with well water for approximately one hour last evening just to be sure it was adequately rinsed. This morning she notes a foreign body sensation. The woman states she also got some of the product in her mouth yesterday which resulted in a bitter taste that has now gone away. On follow up, the woman states her MD discovered a small scratch on her cornea

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							and was given eye medications.
020111 - 00245	8/1/2008	MI	071995-00027-000239	BASIC SOLUTIONS WEED AND GRASS KILLER	103601	MODERATE	A 48 year old female reports that her landlord applied product in yard 3 wks ago. Caller walked barefoot in the yard 2. 5 wks after the product had been applied. That night, caller felt exhausted, developed a migraine headache, itchy eyes, palms and feet were red and itchy (BSA 6%). She developed hives and bleeding with development of scabs on her eyelids. She continued to have insomnia for the past 4 nights. Caller's symptoms have nearly subsided by scrubbing her skin daily with soap and water. She did not seek medical treatment by a physician.
020180 - 00018	4/25/2008	GARDEN GROVE, CA	000524-00445	ROUNDUP READY-TO-USE HERBICIDE (UNSPECIFIED)	103601	MAJOR	A fifty-five (55) year old male allegedly deliberately ingested approximately I 00 milliliters of "Roundup Ready To Use" herbicide, and an unknown amount of acetaminophen with the intent to commit suicide.
020180 - 00023	5/16/2008	FONTANA, CA	000524-00445	ROUNDUP	103601	MODERATE	A twenty-three (23) year old male allegedly was exposed to a "Roundup" product when a sudden gust of wind blew the pesticide onto him, causing skin exposure and inhalation. He was applying it to residential landscape plants on a property in Fontana as part of his father's company's maintenance gardener service. He soon experienced symptoms of dizziness, shivering, weakness, flushing, diarrhea, and later became feverish. The victim drove himself to Pomona Valley Medical Center that evening since it was closer to his home and he was admitted overnight.
020222 - 00001	8/1/2008	IA	000524-00536	ROUNDUP POWERMAX	103601	MODERATE	Caller states, about a month ago he was wearing rubber gloves when he had gotten Roundup Powermax Concentrate poured inside of the glove. The caller states that the concentrate sat in contact with his skin for 2-3 minutes. He did wash the skin off very well at that time. Over the past three weeks, the caller has developed arthritis-like symptoms of his hands.
020223 - 00001	7/1/2008	GA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	A 78 year old female sprayed a lot of Roundup Herbicide, unknown dilution or whether or not it was a ready to use product. She may have inhaled a

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							lot of it. The woman had a sore throat around the time of using the product and now has a chronic cough.
020322 - 00001	10/1/2008	IN	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller states an eight year old child got some Roundup Ready to Use spritzed into his right eye. They have rinsed his eye for about five minutes. The caller is asking if they should they go to the ED. On follow up, the child had been taken to the ED and was diagnosed with a small corneal abrasion per fluorescein stain. The evaluating physician stated the abrasion was not related to the Roundup.
020324 - 00001	9/1/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	A caller sprayed her rose bushes for bugs with malathion. She thinks maybe the wind blew some of the spray back onto her skin. Two weeks later, she went to her PMD with the symptom of a rash on her chin. She has returned to her physician three times and has taken three different pills for her symptoms. She called the malathion people, who thought maybe the symptoms may have been caused by Roundup and was given this number to inquire. The caller had used a sprayer that at some time in the past might have held a Roundup product and then had been rinsed prior to use with malathion. She doesn't really think her symptoms are related to the Roundup. The rash had gone away, but at the time of the call on 1 0/15/08 the symptoms have reappeared.
020326 - 00001	8/1/2008	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states approximately 2 months ago he was using a backpack sprayer at work with an unknown formulation of Roundup Herbicide. It leaked all over his back. He didn't notice that it had leaked and kept working all day long using the backpack sprayer. He did not wash until that evening. He used the backpack sprayer on two more occasions. That day his skin became very hot, a rash developed which comes and goes and itches. Sometimes, his body is numb.
020546 - 00001	8/1/2008	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller's son complained to her last month that he had been feeling ill for some time. Son mentioned that he sprayed some Roundup on plants in his

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							backyard 4 months ago. Caller does not know the type of Roundup that was sprayed or the type of exposure that her son had. Son complained of blurred vision and gastrointestinal problems, sleeping a lot, urinating a lot and blood in stools. He saw a PMD to have medical tests for diabetes which was negative.
020550 - 00001	1/1/2009	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Wife calls to say her husband used Roundup to kill weeds and Triazicide to kill ants about 15 minutes ago. He came inside to eat dinner and approximately 5 to 7 minutes later he had symptoms of his peripheral vision becoming dark; telling his wife he could not see. The wife has rinsed his eye and is wondering if either product caused his symptoms. He may have gotten symptoms from the mist of the product but he has no recollection of the product in his eyes. No direct spray to the eye.
020586 - 00001	1/1/2009	FL	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	An adult male used the Roundup product about 3 to 4 weeks ago. He got it on his hands and has been battling a rash and cracking of skin on the hands. He has been using a product called Lac Hydril cream on his hands without much help. He saw his physician 2 days ago and was prescribed clobetasol cream. On follow up, 4 days later, the rash was improving but seemed to worsen at times. The man had been using Vaseline on his hands along with the clobetasol cream and wearing rubber gloves which seemed to make his symptoms worse. On subsequent follow up, a female family member reports that the man's hands continue to improve greatly. The rash is almost gone. He has been using the clobetasol cream and keeping his hands open to air.
020588 - 00001	5/1/2008	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	An adult male was exposed numerous times spraying fence lines last spring and summer. The man is a part-time farmer and was using a backpack sprayer. The man states he planted corn and then after planting went through the field and fence line with Roundup ready corn. Caller states he has also used a termite control product. The man

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							has been to 8 different physicians to resolve a skin issue. The man states the rash has involved his entire body. The rash moves around, one day it is on his torso and then 2 weeks later it goes to another area. He states his skin welts after scratching. He states he has had constant pain, itching and burning for the past 8 to 10 months. The caller has taken many medications and used topical products with no help.
020638 - 00001	3/1/2009	CA	000524-00343	AQUAMASTER	103601	MODERATE	Caller was riding his bike up and down a hill. The parks service was spraying Aqua Master on the side of the road with a tractor to the right of him. He felt a mist on his face, which tingled a bit. He also thought maybe his face felt numb temporarily. This has subsided. He also got a terrible taste in his mouth. The taste persists despite this happening about 3 hours ago. About 20 minutes after the exposure, he noticed, tremors in his right hand, which have subsided.
020639 - 00001	3/1/2009	TX	071995-00025	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	103601	MODERATE	Caller used Roundup about 5.5 hours prior to calling. She first used a brush to apply before diluting and got some on her hands. She then used the sprayer and got some more on her hands. She did wash off after using the product. The caller also took a vicodin for shoulder pain, which she has taken before, at about the same time as the use of the Roundup. Woman is calling now because she felt faint earlier. She now has vision changes and is jittery. No dermal symptoms.
020725 - 00031	12/2/2008	CA		HONCHO	103601	MODERATE	A 47 (forty-seven) year old male, was exposed to a herbicide and an insecticide (U.S. EPA registration numbers unknown) while he was applying them. He experienced weakness, dizziness, and trouble swallowing and was admitted to the hospital. He was later released two days later. He had been applying and handling pesticides for the last four years without proper pesticide training. In addition, he was not provided with the correct and/or appropriate personal protective equipment at the time of the pesticide exposure.
020770 -	3/25/2009	LAKEPORT, CA	071995-	ROUNDUP WEED	103601	MODERATE	An adult female had post application exposure to

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00001			00025	& GRASS KILLER SUPER CONCENTRATE			the product (applied by gardeners). She experienced rash, cough and brown spots on her skin. She was in bed for three days detoxing with pectin and sulfur glutathione nasal wash.
020795 - 00001	4/1/2009	NC	071995-00023	ROUNDUP WEED & GRASS KILLER1 READY-TO-USE	103601	MODERATE	An adult male mixed product with water and used a pressurized sprayer that malfunctioned, sprayed him in the face, and got the product in his eyes. He then splashed water into his eyes. Several hours later he was still having redness, slight periorbital edema, and discomfort to the eye. He didn't irrigate more than a of couple minutes. He had irrigated his eyes but for a short amount of time but 3.5 hours later he was still complaining of irritation, tearing and some crusting of drainage. The ED MD just looked at his eye visually, no instruments were used. The MD said there was a burn and an infection in both eyes. Antibiotic drops were prescribed.
020796 - 00001	4/13/2009	NV	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller states he used Roundup Ready to Use about 30 minutes ago, when the wind blew some mist back into his face and he accidently inhaled some. Caller states he is having nausea, difficulty breathing, feels short of breath, no vomiting. Caller states he does have a history of COPD. On follow up, the man states he is still having difficulty breathing and stated he had a seizure. Man states he has a history of a seizure disorder. On follow up with the ED after several unsuccessful attempts earlier, the RN states the man had a low dilantin level. He did not have any respiratory symptoms and did not require any breathing treatments. The RN states the man is in the ED frequently and was discharged to home several hours ago.
020800 - 00001	4/5/2009	VA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	A 30 year old adult male suicide attempt (ingested approximately 3oz).
020802 - 00001	4/16/2009	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he used Roundup Concentrate extensively on his property about 2 weeks ago. He mixed it according to the package directions. The man states it had sprinkled rain at least once since he had applied the Roundup. Yesterday, he was digging fence posts in a gravel-like bed where he

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							had previously sprayed the Roundup. It was very windy. The man was wearing boots, gloves, long sleeved shirt and long pants. He noticed his hands were itching and he went in and washed his hands. He states his feet began itching and then he went into 'shock.' The man's wife called an ambulance and he was taken to an ED. He was treated with Benadryl and other "anti allergy stuff' and given intravenous fluids. The man states the physician could find no reason for his symptoms. No bite or sting was noted. The man was discharged to home and now is asymptomatic.
020803 - 00001	4/16/2009	OR	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states she is a first responder from Oregon state calling about herself and her neighbor. Today, the street was sprayed with a combination of 3 herbicides, Glyphosate (Buccaneer), Milestone from Dow chemical and Spyder which contains 'Sulfometuron methyl (applied from a helicopter). She is also concerned about her neighbor that takes Cyclobenzaprine, asking if the chemicals could be interacting with his medication. The caller states she has also been exposed to the same chemicals since she lives on the same street. She has a history of liver disease. The neighbor refuses to go MD or the hospital. The neighbor has a severe headache 'left sided in occipital area with 'brain swelling', 'mastoid swelling neck', and muscle spasms. Onset of symptoms was 2-3 days ago, sometimes he tells her 2-3 weeks ago. The caller states she has had muscle tremors, hot and cold flashes, chills, occipital headache, mastoid swelling, and headache since last week. She states her heart was irregular a couple of days ago.
020813 - 00177	4/17/2009	LITTLE SILVER, NJ	071995-00008-000239	TOTAL KILL WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	A 4 year old male sprayed the product. It was unclear if the child had any exposure to the product. The next day, the child woke up with swollen eyes. He went to MD and was prescribed a steroidal ointment. Two days later he was greatly improved.
020875 - 00002	5/1/2009	NC	071995-00032	ROUNDUP WEED & GRASS KILLER	103601	MODERATE	Caller states 8 year old walked in front of a spray of Roundup Ready to Use Weed and Grass Killer

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				READY-TO-USE			2% about 24 hours ago. He was instructed to go inside and wash it off but evidently did not because he developed rash and itching later. Mother called back several hours later to report that the child developed hives on his legs, abdomen, back and upper arms. He was also started on a new medication last week which he stopped due to a stomach virus but restarted today. The child was evaluated by his pediatrician who administered an antihistamine injection. The MD thought the symptoms may be related to a post viral reaction. Child to follow up with his pediatrician.
020875 - 00003	5/1/2009	NJ	071995-00032	ROUNDUP WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	Caller states that she was using Roundup Ready to Use yesterday and got some of the foam on the back of her hand. She did not think much about it and just wiped off the Roundup instead of washing it off. She reports within a few hours of the exposure, she began to feel tremendously dizzy. She is able to monitor her blood pressure and it was 225/101 mmhg.
020875 - 00005	5/1/2009	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Ophthalmologist calling about a woman that got an unknown formulation of a Roundup concentrate in her eye yesterday. Unknown if immediate first aid provided or not. The eye was diagnosed as having an acid burn with minor corneal staining. Artificial tears recommended. The woman was discharged to home.
020875 - 00006	5/1/2009	NY	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Son calling from the ED with his father being evaluated for sudden onset of short term memory loss and sharp pain in his head. He sprayed Roundup this morning and then at 4 pm, he was talking with a neighbor and all of a sudden didn't remember anything and had a sharp pain in his head. He sprayed the product normally, with no significant exposure. They are currently in an ED, waiting for the MD to evaluate him.
020988 - 00001	7/12/2009	KS	004787-00023	GLYFOS X-TRA HERBICIDE	103601	MODERATE	Caller's husband had been spraying diluted Glyfos X-TRA Herbicide and started to develop flu-like symptoms, fever and chills the next day. Patient sought medical care and was prescribed

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							azithromycin and propoxyphene. According to patient, the medications were not working.
020997 - 00031	6/6/2009	AR	000239-02637	GROUNDCLEAR VEGETATION KILLER CONCENTRATE	103601	MODERATE	A 55 year old male sprayed the diluted product along the driveway and fence. He was wearing shorts. Two days later he developed knee to ankle petechia rash with edema and cellulitis developing. CNP thinks it is a combination product and sun exposure. He was given Prednisone and 2 Decadron injections. He went back to MD because he developed fever/chills/rash/bumps that are now itchy and raised. He was treated with Benadryl and an inhaler for a previous condition. He was also prescribed lincocin.
021052 - 00001	6/1/2009	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states, a few days ago, she became very lethargic and felt like she couldn't get enough oxygen. Her cat also had been sick recently. The caller states she had gone to run an errand and noticed some blue stuff on the ground near where she lives. She called the state department and was told that the product was Roundup.
021060 - 00001	6/1/2009	MS	071995-00017	ROUNDUP CONCENTRATE WEED & GRASS KILLER 1	103601	MODERATE	Caller states he sprayed over 1 gallon of Roundup. It is questionable whether his shirt was damp from the overspray. Caller states it was hot outside. He states there was some overspray on his feet. While spraying, caller states he had a burning spot on his neck which stopped burning when he washed it off. He took a shower 3-4 hours after application. The next day, he woke up itching, a rash on his hands, arms and feet (not like poison ivy) and welts all over him. He had a boiled lobster look. He took Benadryl 25 mg which resolved the symptoms.
021064 - 00001	6/28/2009	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states her 36 year old son had a seizure at church on Sunday 6-28-09. The day before, on Saturday, he sprayed Roundup using a backpack sprayer. It was a windy day. Unknown if any mist blew onto his skin.
021065 - 00001	1/1/2009	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states, for the past year he has had atypical seizure disorder. He is wondering if it could be caused by his exposure to Roundup Weed and Grass Killer. He typically used a 41% glyphosate formulation and diluted it according to directions.

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							He doesn't recall a specific exposure to the chemical. He states he is just trying to rule out causes for his seizures.
021191 - 00021	8/4/2009	IL	000239-02637	GROUNDCLEAR TRIOX TOTAL VEGETATION KILLER 1	103601	MODERATE	An adult male used the product. While he was spraying the hose on his sprayer broke and it sprayed all over his skin. He stated he did wash initially, but now has an infection in his mouth. He has seen a dentist and is being treated. The dentist is not sure of cause of infection.
021244 - 00001	6/1/2009	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller used a Roundup Weed and Grass Killer Pull and Spray product at least 2 months ago. He was spraying around plants. He thought he was sweating, but apparently the sprayer was leaking onto his hand. He did not realize this until after he was done spraying. Since then, he has gotten huge blisters on his hands. He says they are as large as a thumb. He says they're so deep that you can see the muscle. He has been to the doctor and the doctor gave him 2 pills to take, but the pills didn't help. The doctor didn't tell him what was wrong with his hands.
021245 - 00001	8/1/2009	MA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller reports, a neighbor sprayed Roundup unknown concentration diluted 3 ounces to 1 gallon of water, on poison ivy outside the front of her home, approximately 5 yards away. Her windows were open. Within an hour she reports becoming dizzy, experienced a headache unrelieved by ibuprofen, a little relief with aspirin, nausea, shakiness and trembling. Symptoms are better if she lies flat. "Something wrong with her head and spinal cord". She was finally better and then her neighbor sprayed again 6 days later, and the symptoms have started all over again. She feels fine when she is lying down but the symptoms return when she gets up. She denies mishaps or any direct contact with the product.
021247 - 00001	8/1/2009	NC	071995-00032	ROUNDUP WEED AND GRASS KILLER READY TO USE	103601	MODERATE	Caller states that she had been spraying Roundup Ready to Use yesterday and had left the bottle sit on the front porch. At some point, she found her 2 year old grandson with the bottle and he had been spraying the Roundup. He was spitting out acting

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							like there was a bad taste in his mouth at that time. Caller was not concerned at the time but the child woke up with symptom of shaking badly last night at 0300. He is currently sleeping now and has an appointment with his PMD this afternoon.
021250 - 00001	8/1/2009	DE	071995-00023	ROUNDUP WEED & GRASS KILLER 1 READY TO USE	103601	MAJOR	Caller states his 88 year old mother is in the hospital with kidney problems. The son is calling to see if Roundup could be a factor in her illness. He states that in the last 6 months, his mom has used 4 containers of the Roundup Weed and Grass Killer Ready to Use. No actual ingestion, nor dermal exposure. The son is concerned that she may have inhaled some.
021251 - 00001	8/1/2009	MS	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states sometime yesterday, his 5 year old son must have gotten near some Roundup. No further history of any actual exposure available. Child may also have gotten some trash and dirt in his eye this morning while playing outside. This morning, the child's eye was swollen and painful so he couldn't open it. Dad took to him to the emergency department and they diagnosed a big scratch on one eye and prescribed hydrocortisone drops. Now this evening, the child's other eye is painful and swollen. Dad has given an over the counter analgesic and put the child to bed.
021252 - 00001	8/1/2009	SC	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states her spouse was sick with a high fever, dehydration and confusion last week. He is better now. He had good care by the doctor. She states he uses Roundup a lot but is unaware of any specific exposure.
021254 - 00001	7/1/2009	VA	071995-00008	ROUNDUP READY TO USE WEED AND GRASS KILLER	103601	MODERATE	Caller used Roundup in high weeds for 2 days. About two weeks later, he developed a bumpy, itchy rash all over his legs and arms. Approximately a month later, the rash is on his back. No mishaps with the product. He does not recall becoming wet with the product. He has seen a dermatologist for treatment and has had biopsies done. He has been taken off all his medications except his antihypertensive.
021256 - 00001	7/1/2009	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller believes her neighbor upstairs is using Roundup and Miracle Gro. She states she was

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							outside while the neighbor was spraying the other day but denies dermal contact. She is suffering from hoarseness, dizziness, light headedness and skin burning sensation.
021397 - 00001	9/1/2009	CA	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY TO USE	103601	MODERATE	Spouse got Roundup Weed and Grass Killer Ready to Use on his skin. He had on shorts and flip flops. He denies mishaps or spills but was walking thru the weeded area he had treated. No recall of being wet with the product. He suspects he showered the next day. A few days later, he developed a biting sensation on his ankles and feet. At first, he attributed the symptom to insect bites, and started wearing soaks and used mosquito spray. The symptoms worsened and he developed tiny bumps and tiny fluid filled blisters that looked like herpes on the back of his hands. The symptoms then progressed to the dorsum of feet. About 6-7 weeks later, the rash is generalized all over his arms, legs, trunk, buttocks and hands with itchy, weeping blisters and bumps. He saw a dermatologist, who was not sure what it was. The caller mentioned Roundup and she told him that was likely the cause. He has a prescription for a steroid dose pack but had not used it. He is using topical steroids.
021398 - 00001	9/1/2009	WA	071995-00025	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	103601	MAJOR	Call from an emergency crew on scene where an 84 year old male drank Roundup Weed and Grass Killer Super Concentrate approximately 20 minutes prior. His wife found him in the garage when he told her he had intentionally drunk from the 35 ounce container which is now almost one third gone. They estimate 6 ounces ingested;
021401 - 00001	10/1/2009	TN	071995-00032	ROUNDUP WEED AND GRASS KILLER READY TO USE	103601	MODERATE	Caller states that a month or so ago, he was turning the selector nozzle on Roundup Ready to Use when a small amount of the foam got on the corner of his eye. The eyelid, only, was exposed. He remembered thinking that he should wash that off when he was done but he may or may not have rinsed it. About a day later, he began to have a minor itch at the exposed site and peeling skin

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							from that area. Both symptoms persist to today. He has applied hydrocortisone cream to the area maybe once or twice.
021466 - 00001	11/1/2009	ND	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller stated he used a concentrate Roundup Weed Killer for farming, trying to kill trees. He is unsure how it was diluted. He had a typical overspray exposure, and showered at the end of the day. Two days later, he got out of bed and fell. He was seen in the emergency department and was diagnosed as having Guillain-Barre. He went to the Mayo Clinic, 2 months ago, and was told his symptoms are consistent with Guillain-Barre. He is still having muscle weakness in his legs.
021610 - 00001	1/23/2010	HI	000524-00475	ROUNDUP PRO	103601	DEATH	49 yr. old Hawaiian man intentionally ingested Roundup Pro, death. ER staff said there was nothing they could do
021635 - 00001	9/1/2009	NJ	071995-00025	ROUNDUP WEED & GRASS KILLER SUPER CONCENTRATE	103601	MODERATE	Caller states about 4 months ago some diluted Roundup Weed and Grass Killer Super Concentrate splashed on his leg when he was applying the product. He did not wash it off until later when he started having burning and stinging on his legs. He has been to two different dermatologists and his PMD over the past 4 months and has been given three different creams that have not gotten rid of the burning sensation. The symptom is still present off and on.
021635 - 00002	11/1/2009	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states she sprayed weeds with an unknown type of Roundup less than 2 months ago. She used one glove for pulling weeds that were sprayed with the Roundup and then folded her arms while talking to neighbors. She developed a rash on the upper arm area several days later and the rash has remained since then. She is under the care of a dermatologist who cannot say what the cause is. The area is red now. It started as a mosquito bite like nodule, hard boil, and dime size bumps under her skin. She never had any blistery rash.
021817 - 00001	3/23/2010	CA	000524-00445	ROUNDUP HERBICIDE FROM MONSANTO	103601	MODERATE	Caller states that about one month ago, her gardener applied an unknown formulation of Roundup from a golf course to her weeds outside. Her small dog was outside running in that area the

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							next day and developed small pinpoint lesions on its face which seemed to bother the dog by itching. After holding the dog, she too has developed pinpoint bumps with craters in them, which are extremely pruritic on her arms. She has seen a dermatologist and they have done biopsies which are pending.
021819 - 00001	3/6/2009	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states, in the spring a year ago, she was using a Roundup product at work. Some went onto her pant leg and into her sock. Some went onto her ankle which she wiped off with a wet paper towel and soap soon afterwards. Since then she has had an intermittent rash on her ankle that gets dark when she scratches it. She has consulted her PMD.
021898 - 00001	4/9/2010	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller used a Roundup product 2 weeks ago. She got some into her eye and it burned, so she flushed it for 1-2 minutes with water. Seven days ago, she noticed large floaters in her eye. She contacted her PMD, who told her to see an eye doctor immediately, but she didn't. Today, she has thousands of black spots that she sees. Caller states symptom came on suddenly. Eyes feel dry and hurt.
021899 - 00001	3/26/2010	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states she used Roundup more than 1 month ago. She vaguely remembers a drip getting onto her hand or wrist area. She doesn't think she washed it off right away because it was such a minimal amount. For several weeks, she has had an area on the top of her wrist that is a patch of bumps that resembles poison ivy and weeps a yellowy discharge. It itches and appears to be gradually getter larger. It started out looking like 4-5 bug bites, but it has progressively gotten worse. She is going to MD next week.
021900 - 00001	4/15/2010	CO	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY TO USE	103601	MODERATE	Ophthalmologist is seeing a 39 year old male with a complaint of pupil dilation in one eye only. In trying to determine the cause, the man reports using Roundup Weed and Grass Killer Ready to Use, four days ago. He is not aware of getting any in his eyes, but states it might have blown there.

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							No complaint of eye irritation or redness at the time of use.
021902 - 00001	3/24/2010	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller notes that several weeks ago she was using Roundup concentrate (6 ounces to 1 gallon) dilution and then also mixed it (12 oz to 1 gallon). Some was sprayed on her hands and legs when her sprayer got clogged. She has been noticing muscle spasms to her hands, feet, and legs and urinary incontinence.
021983 - 00001	5/15/2010	MO	042750-00061-072693	CROP SURE GLYPHOSATE PLUS	103601	MODERATE	An adult male indicates he was exposed to the product 2 weeks ago. He was sitting on an ATV seat saturated with diluted product. He reports he developed a severe rash all over my body. He saw a doctor and was placed on the oral antibiotic doxycycline. The caller also reports he had developed diarrhea for three days following the dermal exposure described. The caller is ASX at this point.
021983 - 00002	5/24/2010	IL	042750-00061-072693	CROP SMART GLYPHOSATE 41 PLUS	103601	MODERATE	An adult male states that product spilled on his leg one week ago. Two days ago his wife noticed some swelling in his lower legs.
021990 - 00001	5/9/2010	AZ	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY-TO-USE	103601	MODERATE	Caller states that he got Roundup Ready to Use (unknown formulation) on him this past January (approximately 4 months ago). It sprayed on him when he opened the container. Caller states he has had symptoms of numbness and swelling of tongue and lack of taste since the exposure.
021991 - 00001	5/14/2010	TX	000524-00454	HONCHO PLUS HERBICIDE	103601	MODERATE	Man works at a tractor supply store and has become sensitive to some chemicals he works with at the job. Last evening, he was mixing Honcho Plus around 6-6:30 pm, getting the concentrate on his hands while mixing. He did rinse with water promptly and later with soap and water. He did feel burning on his hands at the point of contact but no rash or redness noted after rinsing with water. Around 10 pm when his spouse saw him at home, he was disoriented and confused, she brought him to the local ER.
021992 - 00001	5/11/2010	MO	071995-00017	ROUNDUP CONCENTRATE WEED AND	103601	MODERATE	Man sprayed Roundup on his property today. No known exposure. Tonight he is having significant symptoms but refuses to be checked out at the ED.

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				GRASS KILLER 1			He has symptoms of dizziness, walking into walls, drowsiness, and ataxia.
021993 - 00001	5/5/2010	OH	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY-TO-USE	103601	MODERATE	Caller used a Roundup Ready to Use product, 2 days ago in her yard. No mishaps during use. Yesterday, she was working in her yard in the area she had sprayed the day prior and noticed her hand was itching. Then the back of her neck, and legs broke out. She has generalized hives, swelling and itching. She is concerned she came in contact with the Roundup and worried that it is causing her symptoms.
021994 - 00001	5/28/2010	MO	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY-TO-USE	103601	MODERATE	Woman used Roundup Weed and Grass Killer Ready to Use 2 days ago, getting some on her hands and spilling some on her feet while pouring it from one container to another. The smell of the product makes her feel lightheaded. She did wash well but did not feel well later in the day, becoming nauseated and continued to be nauseated. She was at the dentist office yesterday. She had her BP checked at 83/58. Today, her fingertips are numb. She denies history of medical problems. She did not ingest any Roundup.
022100 - 00001	6/19/2010	HI	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Call from Hawaii at a hardware store where 2 days ago, a weed killer that was in a sprayer device was returned to the store. It was evidently sprayed on the arm of an employee at that time. She did not get to wash it off right away but rinsed a few minutes later. She states the customer told her it contained Roundup, but there was no way to verify what was in the container. The employee complains of a red, flushed look to her arm and leg (leg was not sprayed). She feels a funny tingling type sensation to the skin, and complains of chest pain and shortness of breath.
022101 - 00001	6/18/2010	OH	071995-00032	ROUNDUP WEED AND GRASS KILLER - READY TO USE	103601	MODERATE	Caller states, 2 days ago her friend sprayed Roundup Ready to Use on some very tall weeds. The day after spraying, she started to have trouble breathing and can hardly walk now, without becoming winded. The friend thinks that she may have breathed in some of the mist while spraying the Roundup.

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022102 - 00001	6/30/2010	NY	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	Call coming from Syracuse EMS and they are en route to a home where an adult male is unconscious and has been reportedly using Roundup all day. No other details are known, caller wants to know what type of herbicide is in the Roundup and if it would cause this type of symptom.
022103 - 00001	6/24/2010	MO	000524-00454	BUCCANEER PLUS HERBICIDE	103601	MODERATE	Caller states she was spraying with Buccaneer Plus about May 25th in her yard. It was diluted to label directions. She sprayed for about 3 hours then came in and took a shower. The day before she knew she had been around poison ivy and started itching. MD prescribed her Prednisone. Since then, she has seen MD about 4 times. She says her skin is swollen from head to toe for one week. Her skin appeared to be turning orange from a burn, the past 4 days, with some skin peeling. MD asked her if she was exposed to herbicides and is treating her now with Bactrim to 'get poison out of her '.On follow up the nurse practitioner stated she did not feel the woman's symptoms were related to the Buccaneer Plus.
022175 - 00002	7/8/2010	ALTOONA, PA	053883-00059	SURRENDER ERASER SYSTEMIC WEED & GRASS KILLER	103601	MODERATE	A 17 year old male sprayed this product outdoors using a backpack sprayer for about 3 hrs. He was not wearing any PPE, just shorts and a t-shirt. Some of the product spilled down the back of his shirt. He showered that night as usual, but woke up the following morning with 'flu-like symptoms' as well as some muscle and joint pain. No fever or other symptoms. Although he was "80% better," three days later he saw his MD. No specific treatment was rendered at that time as he was getting better on his own.
022192 - 00002	7/28/2010		000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states her husband was spraying Roundup concentrate. The wind was blowing while spraying. She found her husband lying on the grass. She got him inside and he took a shower. His nose is congested.
022192 - 00003	7/17/2010	MO	071995-00018	ROUNDUP WEED AND GRASS KILLER 1-SUPER CONCENTRATE	103601	MODERATE	Woman presents to the ER with a complaint of numbness to both legs and difficulty urinating. She is able to go only small amounts since Wednesday. The RN believes, on Wednesday, the woman was

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							using Roundup concentrate that she had diluted and got some on her feet. There are few details of the exposure. The woman denies using any other chemicals.
022192 - 00005	7/20/2010	CT	071995-00023	ROUNDUP READY TO USE POISON IVY AND TOUGH BRUSH KILLER 3	103601	MODERATE	Caller states he spilled some Roundup Ready to Use Poison Ivy and Tough Brush Killer 3 on his thumb about 30 minutes ago. At the time of exposure, he used hand sanitizer to rub it off. About 10 minutes later, he washed with water and soap for 5-10 minutes. He notes some redness on his skin just below his wrist but not on his thumb at the point of contact. He states he feels tingling of the hand and is dizzy. On follow up, the man stated he was at the emergency room because he was short of breath and felt like he was going to pass out from being dizzy. He states his tongue went white and his mouth was dry.
022192 - 00007	7/1/2010	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller and her sister are elderly. They have an absentee landlord neighbor whose lot adjoins theirs. In the middle part of April, he sprayed the grass between their homes. They began having symptoms at that time. Symptoms experienced were, sore throat with "pus sacs" and red pimples down the throat, burning sensation in the skin and coming up out of the esophagus, abdominal cramping, vomiting, itching, hair loss and headaches. Their MD gave them a Z pack antibiotic, and eventually they were doing all right. On the 24th of May they saw the neighbor out spraying and then leaving. They felt stinging of their eyes and skin, respiratory irritation, dizziness at the time of spraying. They got another Z pack antibiotic from PMD afterwards.
022193 - 00002	1/1/2010	KAUNAKAKAI, MOLOKAI, HI		ROUNDUP	103601	C,MODERATE	Roundup sprayed near female AA member: malaise, sinus discharge, Part vague: mentions death nearby after Roundup was used
022193 - 00003	11/1/2009	MOLOKAI, HI		ROUNDUP	103601	DEATH	Roundup sprayed near female AA member: malaise, sinus discharge, Part vague: mentions death nearby after Roundup was used
022268 - 00001	8/30/2010	VA	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	Caller states her sister-in -law drank a pint of Roundup - unknown formulation yesterday. The

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							woman was out on pass from a psychiatric center and when she returned she was vomiting.
022270 - 00001	8/2/2010	IL	071995-00032	ROUNDUP WEED AND GRASS KILLER-READY TO USE	103601	MODERATE	Woman spraying the Roundup Ready to Use this afternoon and thinks that she got some on her hand and then rubbed it into her eye. Tonight, her eye is very irritated and is lachrymating. Woman has removed her contact lens. On follow up the next morning, the woman went to her eye doctor early in the morning and was diagnosed with severe chemical burn to the cornea. The doctor prescribed antibiotics. It was noted that at the time of the exposure, the caller had no burning sensation or irritation.
022271 - 00001	8/31/2010	VA	071995-00032	ROUNDUP WEED AND GRASS KILLER-READY TO USE	103601	MODERATE	Caller states that his father was using Roundup Ready to Use yesterday and got some of the spray in his hair. He did shampoo his hair soon after the exposure. At some point he was reading a newspaper and has a habit of licking his finger to help turn the page. When he licked his finger he noted immediately the left side of his tongue went very numb. He woke up this morning with left sided facial drooping and his left eyelid is drooping.
022272 - 00014	7/22/2010	DE	071995-00008-000239	TOTAL KILL WEED & GRASS KILLER READY-TO-USE	103601	MODERATE	An adult female got some of this on her legs. Then 2 days later she developed blisters on her leg. She thought it was just poison ivy. She used a steroid cream on her symptoms and the blisters went away. Then it turned into a big bubble so she went to MD and they gave Death oral steroids. She now has scars on her leg. She was calling to see if it might be related to the product.
022395 - 00001	9/17/2010	FL	071995-00025	ROUNDUP WEED AND GRASS KILLER SUPER CONCENTRATE	103601	MODERATE	An adult male had mixed a total of 15 gallons using Roundup Super Concentrate, dilution of 3 ounces of concentrate per gallon of water to apply over 15 acres. He has a large container on the back of his pickup truck and he used a sprayer hose to spray the Roundup. There was an occasional wind shift and he got the product mist on his skin. He was spraying for approximately 6 hours. He had hives that started in the groin area. His feet began to itch and then he had welts all over. He was

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							treated with Benadryl and had an appointment with his MD the next day.
022401 - 00001	9/1/2010	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Wife calling after being prompted by nurse to question pesticide encephalopathy. Her husband used Roundup 4 days ago. The son brought the product over stating it is Roundup in a spray bottle. The caller does not have the label, ingredients or dilution available. Her husband eyes were swollen the day after use. His symptoms have progressively gotten worse. He started with a headache, now he is disoriented with hallucinations, left arm and leg numbness. The caller has taken her spouse to the hospital 3 times. All CT scans do not show sign of stroke. Her husband's PA just keeps sending them back to the hospital. The man does not take any maintenance medications.
022453 - 00001	10/6/2010	TN	071995-00032	ROUNDUP WEED AND GRASS KILLER-READY TO USE	103601	MODERATE	Caller states that his wife was helping him spray Roundup Ready to Use about 4 weeks ago. She was holding up a sheet of tin foil that they were using to shield plants that they did not want sprayed. No known exposure to the Roundup at that time. Three to four days later, she started with symptoms of a rash on her chest, which has spread to her face. They have gone to their PMD and since have been referred to a dermatologist. She is on Prednisone and various creams. Biopsy of the rash was done this week.
022454 - 00001	########	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Ace Hardware employee calling on behalf of a customer who got a mist of an unknown formulation of Roundup in his face about 20 minutes ago. He has developed chest pressure.
022504 - 00001	11/8/2010	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Physician office calling about a man that has been using diluted Roundup every day for 3 months while wearing gloves but sometimes touches his face. His skin is red and swollen with blisters.
022805 - 00001	10/1/2010	OH	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY-TO-USE	103601	MODERATE	Woman calling in regards to an indirect exposure to a Roundup Weed and Grass Killer product. She had used the product indoors to treat and is now calling due to the eruption of red raised lesion to the back of her leg which occurred following exposure and had then spread to her neck, arms as

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							well as her waist. The caller stated that she has been in to see dermatology and was given steroid injections which essentially eradicated the condition with only an occasional outbreak. Now she is calling just in case the rash may be related.
022938 - 00002	4/14/2011	PR	000524-00475	ROUNDUP ULTRA	103601	MODERATE	Caller is from Puerto Rico. Spanish translator conferenced on the line. The translator states the caller used Roundup Ultra 2 months ago. He got a spray of the diluted product on his forearm. Since that time, he has been nauseated and had a burning stomach. No oral ingestion. No rashes noted post exposure. No chest symptoms. He has seen a cardiologist. He would like to know what to take to fix these symptoms. MRPC discussed the product toxicity. The symptoms do not correlate with the expected response to the product. Advised to continue under the care of his PMD. MRPC is available to speak to the MD if desired.
022938 - 00004	4/15/2011	NE	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states his 14 year old gardener sprayed Roundup last week and broke out in hives from head to toe that evening. The teen had used it all last summer with no reaction. MRPC discussed the product toxicity. The symptom does not correlate with the expected response to the product. Advised to have the family or MD contact MRPC if further concerns.
022938 - 00005	4/15/2011	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Son calling, about his 70 year old father who accidently drank less than a mouthful of Roundup about a week ago. The father thinks he spit most of it out. The caller states that they are taking him to the hospital tonight because he is still having symptoms. The caller does not know what the specific product was. He knows that it was a diluted concentrate. The caller states his father's gums and the top of his mouth are sore and painful. His father has been seen once before today. The physician told him that he had 'pus pockets' in his mouth. He also had areas of irritation in his mouth that were bleeding. His father is now complaining that his stomach is hurting. MRPC discussed the product toxicity.

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							Delayed onset abdominal pain is not an expected response to the product. Advised to observe for worsening of symptoms. On follow up, spoke with the daughter-in-law. The man is in the hospital. Running some tests. The MD thinks it may be some sort of chemical burn. PCC is available to provide information about the active ingredient or consult if the MD desires. No return calls received.
022938 - 00006	4/20/2011	TN	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY TO USE	103601	MODERATE	Caller states that on 3/11/11, he was spraying a Roundup Ready to Use product. He felt liquid on his right thigh through his work jeans. He washed the area within 30 minutes. 5 days later he had chills, different muscle twitches. His twitches are mostly gone and his chills are resolved. Now he has a burning sensation at the site for less then a week. The caller is unable to find the ingredients on the label he had saved. MRPC discussed the product toxicity. The symptoms do not correspond with expected response to the product. Advised to follow up with PMD if his symptoms persist or worsen.
022938 - 00007	2/1/2011	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Mother of a 27 year old female notes that she believes her daughter's ex-husband may have been poisoning her with Roundup. The last contact with him would have been February and no contact with him since then. The woman states that they have been researching different things and she may have been poisoned by a concentrated type of product. Ate food twice prior to February that tasted strange. MD is involved and not sure of what was ingested or if it is a poisoning or medical problem. Also notes other products such as WD40 come up missing from the home. She complains of hives, mouth burning, stomach upset, poor PO intake, vomiting, diarrhea, and blue nails.
022938 - 00008	4/28/2011	GA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Dad calls about 11 year old daughter who lost some vision in one eye. She is currently in CT scan for evaluation of the eye now. Caller states about a week or 2 earlier, he had sprayed the ground with diluted Roundup. This past Monday night and today, his daughter had planted some flowers. She

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							may have rubbed her eye with her hand. He is asking if that could affect her vision. MRPC discussed the product toxicity. The symptoms do not correspond with expected response to the product. SPI concerned re: possible misinterpretation of symptoms and/or possible misidentification of product or mixed exposure.
023018 - 00001	5/21/2011	CA	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 READY TO USE	103601	MODERATE	Caller states that she already had a pre-existing case of productive bronchitis. On this past Wednesday, when she sprayed about 3/4th of a gallon of Roundup Ready to Use formulation, her bronchitis turned into wheezing. She did a nebulization treatment that she had in her home. After doing a treatment with no improvement she involved her PMD and is now hospitalized. Her breathing status has gotten worse.
023018 - 00005	5/2/2011	GA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states his brother had been spraying Roundup outside earlier today and ' had a seizure' about an hour ago. No history of seizures before. No product known to be on skin or ingested. The man had diarrhea, a seizure and fell in the bathroom.
023052 - 00001	6/3/2011	TN	000524-00454	HONCHO PLUS HERBICIDE	103601	MODERATE	One month ago, the man was spraying an apple tree using a water mixture of Honcho Plus. He got some overspray on his head and was not wearing a hat that day. He has a raised itchy rash on his scalp. He saw his doctor today who recommended he cut his hair short and recommended a topical treatment. On follow up, 3 days later, the man states, he used hydrocortisone cream as directed. It has helped the itching but the raised bumps are still there. His doctor diagnosed them as seborrheic dermatitis and that he should cut his hair short for it to get better. The Honcho Plus probably did not cause this.
023052 - 00002	6/6/2011	HI	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller is concerned about her brother who uses Roundup and was just diagnosed with bone marrow cancer. Caller questions if benzene is in Roundup
023052 - 00005	6/22/2011	PA	000524-00454-	GLY-4 PLUS HERBICIDE	103601	MODERATE	Caller states she was misted with water diluted Gly -4 Plus Roundup when she was on a tractor

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			072693				mowing a neighbor's lawn and man went by spraying at distance away, of a semi-tractor trailer. She could feel the mist on her body and can still see it on her sunglasses that she had on that day. She started to cough and her throat was burning. She stopped and went inside and rinsed out her mouth. She went to an ER that night because she could not stop coughing. She was told she was being treated for chemical burns to her throat and lungs. She was given nebulizer treatments, flovent, albuterol, diphenhydramine x 2 Q 4 hours and steroids. Two days later, she got on the same mower and within 5 minutes the symptoms developed again and she was treated in the ER. About 5 weeks later, she is doing better but her throat is still sore. No known allergies or history of asthma.
023052 - 00006	6/23/2011	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states her spouse was exposed to the spray of Roundup when the wind shifted during spraying about 1 year ago. No mask was worn. He has had problems with his breathing and nose bleeds since then. The man bathed after the exposure. He had diluted the Roundup- 2 quarts in 25 gallons of water. Since that time he has had bronchitis. 15 days later he had a nose bleed that bled 5-6 times/day for over a week. The man has a long standing history of nose bleeds since childhood. The ENT MD performed a cauterization. He remained flat on his back for several weeks using nasal gel and antibiotics. About 6-7 wks ago, the man became ill and went to the MD and was given levaquin for treatment of pneumonia, although his lungs were clear. He got better, when the levaquin ran out, his symptoms got worse. He was given prednisone and cough syrup for bronchospasms. His lungs are clear per CXR. When the steroid was gone he got worse again. He is now seeing a pulmonary specialist and given more antibiotics and now has a fever.
023177 - 00001	7/18/2011	CA	000524-00475	ROUNDUP PRO	103601	MODERATE	Caller states he was spraying for approximately 1 week with diluted Roundup Pro. The wind was

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							blowing, but he did not feel he got any on him. He wore a mask while spraying. He went to the MD for an earache but there was no ear infection. Complaint of a headache and some ataxia.
023183 - 00001	7/2/2011	CO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states 80 year old male who used Roundup yesterday was exposed dermally to the mist. The man did not wash the area with soap and water. The man is experiencing nausea, stomach cramps and chest pain.
023208 - 00001	7/27/2011	TX	071995-00023	ROUNDUP WEED & GRASS KILLER 1 READY TO USE	103601	MODERATE	Caller states she used Roundup Weed and Grass Killer Ready to Use yesterday. The woman states it was very hot and she was sweating a lot. She used a handkerchief to wipe her face. Her eyes started to burn and continued after closing her eyes. She instilled natural tears. Today, she is having trouble seeing, particularly out of one part of her eye. On follow up, the woman states she went to the ophthalmologist, who says she has a scratch on each eye. She has a prescription for erythromycin drops, and one for Tobradex. Her vision was improved.
023262 - 00001	8/23/2011	NC	071995-00023	ROUNDUP WEED AND GRASS KILLER 1 - READY TO USE	103601	MODERATE	Caller states he used Roundup that 'kills poison ivy ' one month ago on some weeds by his home. He states it has rained 3 times fairly hard since that application. Every time he gets out of his car and walks by this area, he states his nose and throat bums. The man called back again for the phone number to the company to inquire how to remove the product from the air. The man called back later, stating he continues to have eye and throat burning in spite of having several hard rains in his area. He states that he can hardly breathe and just feels 'sick'. Unable to name details other than he feels sick. The caller has not phoned his physician or the product line as recommended previously.
023265 - 00001	8/2/2011	IL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that an unknown formulation of Roundup was sprayed on a weeded area and a bush area in his apartment complex for 2 days in a row. The caller states when he steps outside the door he's affected. He has had no direct exposure to the

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							Roundup, but he walks by the sprayed areas. He states he cannot get the MSDS from the complex. No air conditioning in the apartment. The caller has a history of epilepsy and is a smoker. He states he has been having seizures everyday since the spraying. He is losing his appetite and has lost 6 pounds since last Thursday. When he spits, blood comes out of his esophagus. The caller states when he does not go on the property, he is fine.
023266 - 00001	8/15/2011	MN	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller is calling on behalf of her father-in-law. He used Roundup on July 9th. Since then, he started experiencing tingling of his hands, arms, feet and lightheadedness. He keeps touching skin and saying it looks different. The caller cannot see a change in her father-in-law's skin. The man has been evaluated for heavy metals and toxins. His doctor could not find anything wrong with him or no medical cause of these symptoms and advised the man to call the poison center. A CAT scan and MRI and artery testing revealed nothing. The man also seems lethargic and quiet when he used to be full of life. To the caller's knowledge, the man put concentrate in another bottle and added water. He sprayed it in cracks of the sidewalk, around the pool shed. The wind was blowing, so any exposure would have just been from overspray. He showered that day, but it could have been hours after spraying.
023267 - 00001	8/21/2011	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	ER calling about 22 year old male that arrived by EMS and states he ingested 2 mouthfuls of an unknown formulation of Roundup that was in soda bottle where he is staying about 24 hours prior. Apparently, the man had no complaints until tonight. His tongue is white without ulcerations; the nurse says it looks like thrush on the tongue. His pupils were large, no history of vomiting or diarrhea. En route to ER, EMS reported the man to be posturing and foaming at the mouth. One liter of LR given IV. The man is talking nonstop "all over the place" at this time. The man was admitted to the HCF for seizure precautions and monitoring.

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							Labs were within normal limits. He had a complaint of his throat being sore and also reported that he did vomit twice but unknown when he actually vomited. The next day the man had no further complaints, stable vital signs, no GLC symptoms or seizure activity.
023361 - 00001	6/22/2011	WA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that 3 months ago, a lawn care company sprayed an unknown Roundup product on his lawn. A day or a few days later, he worked in the yard on his knees. Later, he thought, he must have had the product soak up through his pants because he developed a blister on his knee. He called his PMD and dermatologist immediately, who were both booked up solid. He went to the pharmacy where they recommended hydrocortisone cream, which he has been using since that time. Symptoms of blistered swollen knee, extending to the waist is present. No itching is noted.
023364 - 00001	9/24/2011	AZ	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	man intentionally drank 150-350 ml concentrated Roundup Herbicide with vodka; he was found and taken to ER; hypotension requiring vasopressors which resulted in increased lactate leading to metabolic acidosis, evidence of renal impairment. Man showed signs of improvement by day 4 post exposure.
023365 - 00001	9/12/2010	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Man calling is 44 years old, with a history of a traumatic brain injury in 2006 which has resulted in balance and equilibrium issues. He has difficulty walking which has worsened over the last year with increasing muscle spasms to the point he can no longer walk. His symptoms are similar to those of MS. He recently learned that the marijuana he had smoked 8 to 12 months ago had been killed with Roundup.
023531 - 00001	6/14/2011	NM	000524-00517	RANGER PRO	103601	MODERATE	Nurse practitioner calling from a PMD office where a 67 year old male is being seen for the third time in the recent past. He has been using Ranger Pro 8 to1 0 times between 3 to 5 months ago. The last time he used the product was about 3 months ago. He dilutes the product 5 ounces into 1 gallon.

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							He did get the diluted product on his ankle 5 months ago. He was wearing shoes (not sandals) with no socks. He did not wash off until the next day with his normal morning shower. He had a stripe of redness on the top of his left foot and developed joint pain of his left ankle. Since that time he has had hives on his right forearm, a red raised rash of his axilla area. He has been on a medrol dose pack.
023532 - 00001	########	CA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states his 82 year old dad was mixing one of the concentrate Roundup products with water 6 months ago and spilled some on his finger but did not wash it off right away. Unknown if he spilled the concentrate or the dilution on his finger. Blisters appeared on the finger but the caller does not know the time frame of onset. Since then, he has had a burning pain in the finger. The skin is now completely normal.
023577 - 00001	8/6/2011	NEW ORLEANS, LA	042750-00061	GLY STAR PLUS	103601	MINOR	An adult male got the product in his eye. He experienced vision problems. He went to three MDs. He was not able to resolve his symptoms.
023628 - 00001	########	BROKEN BOW, OK	042750-00060	GLY STAR ORIGINAL	103601	MODERATE	An adult male got the product in his eye. He experienced vision problems.
023704 - 00001	12/8/2011	CAPE CORAL, FL	042750-00061	GLY STAR PRO	103601	MINOR	An adult male go the product on his hands. He did not rinse his skin right away. His skin became dried and cracked.
023710 - 00001	1/23/2011	WV	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Woman calls from West Virginia about her exposure to an unknown formulation of Roundup one year ago. She was sitting on Main Street on a windy day when she noticed a misting on her face and skin. At the same time, the railroad was applying Roundup to the weeded areas on their property. She came home and called the railroad office to see what they were using and was told 'Roundup' but no particular formulation. She feels she was 'heavily sprayed' but showered within 1-2 hrs of the exposure when she got home. The only concern she offers is that her skin seems like it was 'burned' in several places and has been peeling.
023821 - 00001	10/1/2011	MI	000524-00445	ROUNDUP ORIGINAL	103601	MODERATE	5 crew members were in a field in MI doing a survey project. The field was adjacent to a farm. A

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							contractor sprayed 2 fields next to workers with roundup. Workers had multiple symptoms. Headache, nausea, burning of eyes, nose, throat, metallic taste in mouth. Decontaminated within 1 hour of exposure. Symptoms resolved 1.5 hours after decontamination.
023906 - 00001	3/31/2012	IN	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he was spraying an unknown formulation of Roundup that was diluted to a stronger strength than what is instructed. The sprayer hose came off and sprayed the product in his mouth, face and eyes an hour ago. He showered and flushed his eyes for 30 minutes. He has rinsed his eyes every 15 minutes since then. His eyes are burning. He drank 2 glasses of chocolate milk. He is calling now because he is dizzy and feels his speech is slurred. Adequate dermal, PO and ocular irrigation were performed.
024028 - 00001	4/21/2012	MO	071995-00023	ROUNDUP WEED & GRASS KILLER 1 READY TO USE	103601	MAJOR	Caller notes that on Monday his wife was out spraying with some type of Roundup Ready To Use. It spilled and made the back of her shirt wet. On Friday, they found out that she experienced a miscarriage. The caller is asking if this was related to her exposure on Monday.
024028 - 00002	4/20/2012	MO	071995-00023	ROUNDUP WEED & GRASS KILLER 1 READY TO USE	103601	MODERATE	Caller states this past Tuesday afternoon, his wife began to have involuntary movements of her left arm and leg, which now looks as if it is moving to her right side, and her speech and thought process were altered. The caller phoned her PMD who referred her into an ED and she was admitted to the hospital. She has had a stroke work up, CT scan and MRI. The caller is inquiring about the use of Roundup.
024172 - 00001	5/18/2012	OK	071995-00016	ROUNDUP SURE SHOT FOAM	103601	MODERATE	Caller states she used a whole container of Roundup Sure Shot Foam last evening on the weeds when some came back on her. She did not think much of it and did not take a shower until later that night. She has used Roundup in the past without any problems. The caller is covered with hives from her waist to her knees. No trouble swallowing and no swelling. MRPC discussed the product toxicity. Possible allergic reaction to an

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							ingredient if the woman is hypersensitive. The woman is planning on going to the ER for treatment. She does not have any Benadryl at home. On follow up, the woman was taking Benadryl and applied Caladryl. The woman is feeling better and her symptoms are improving. Woman states it was a windy day and she may have inhaled some of the mist.
024172 - 00003	5/17/2012	MD	071995-00032	ROUNDUP READY TO USE POISON IVY AND TOUGH BRUSH KILLER 2	103601	MODERATE	Man calling to rule out all causes of his symptoms of shortness of breath and nausea that he has experienced for the past 1 week. He has been to the ER and the symptoms are non cardiac related. Last week, he used an old bottle of Roundup Poison Ivy and Brush Killer RTU formula. The bottle was in the garage for a few years. The sprayer leaked and got on his hands and arms for 5 minutes only. He washed off promptly. MRPC discussed the product toxicity. The symptoms do not correlate with the expected response to the product.
024172 - 00007	5/16/2012	ID	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Ophthalmologist calling with vague details. He is seeing an adult male, who got Roundup splashed into an eye a couple of days ago. Unsure of the exact Roundup product or if a concentrate or diluted formulation. He is unsure if there was even an ocular exposure to Roundup. No irrigation done by the man at the time of the exposure. His eyelid is very swollen and part of his cornea has come off. MRPC discussed the product toxicity. The symptom does not correspond with the expected response to the product. Caller declined to have the product information faxed to him or to give information on the person that was exposed.
024172 - 00008	5/21/2012	IA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that her husband had been spraying an unknown formulation of diluted professional Roundup on the farm this past Thursday. He got some on his hands and did not wash if off for about 5 minutes. On Thursday evening into Friday morning he began to have tightness of his chest and he broke out into hives. He went to the ED and had a cardiac work up which was negative. He took Benadryl for the hives and they dissipated. Today

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							he started with the hives again and in addition he is having swelling of his hands and feet. MRPC discussed the product toxicity. The symptoms do not correspond with the expected response to the product. Advised to stay under medical care of MD.
024172 - 00009	5/30/2012	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	RN calling from ER about a farmer, who had been spraying with an unknown formulation of Roundup for a couple of hours about 3.5 hours ago. Afterwards, he was talking to a friend, and started having slurred speech and according to his friend, he seemed to "zone out for a minute". RN states since arrival to the ER, the man has been awake and alert, oriented x 3, vital signs have been stable and within normal limits. No slurred speech noted. MRPC discussed the product toxicity. The symptoms are not consistent with the expected response to the product. The man was discharged to home within a few hours of arrival.
024222 - 00001	4/25/2012	PR	000869-00238	GREEN LIGHT COM-PLEET 41% SYSTEMIC GRASS & WEED KILLER 2	103601	MODERATE	A male used the product and experienced an all over body rash. He was seen by a medical facility and subsequently was treated the rash. The medical facility advised the rash would go away and the caller should have no lasting effects from the rash. Caller wanting to know if this is truthful information from the medical center. One week later he still had the rash.
024294 - 00004	6/5/2012	MO	000524-00454	BUCCANEER PLUS HERBICIDE	103601	MODERATE	Caller used Buccaneer Plus yesterday that he mixed in a 30 gallon sprayer to pull behind his lawnmower. He mixed 1/2 gallon of the solution in 25 gallons of water. No mishaps, although may have been exposed to some of the overspray. He does not recall significant wetness of his skin or clothes from the Buccaneer. He also burned a citronella type candle in his home last night. He broke out in hives last night with mild itching. He took a Loratadine 10 mg tablet earlier today.
024294 - 00005	6/20/2012	TX	000524-00475	ROUNDUP PRO	103601	MODERATE	Nurse calling from an occupational clinic about a 44 year old male who had an exposure to diluted Roundup Pro 30 minutes ago. The man was getting ready to use his rig he had prepared 2 days prior for

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							spraying. It had Roundup Pro inside the tank diluted 34 oz to 55 gallons of water. He went to turn it on and the hose popped off and sprayed him in his face, eyes and chest area. He had safety goggles on. They have been rinsing his eyes for 15 minutes. He is complaining of a skin burning sensation and throat irritation. On follow up, the nurse states the man complains of slight blurring of vision. On further follow up, it was noted that the man had a corneal abrasion. He was given eye drops and discharged to home.
024309 - 00002	6/18/2012	OROVILLE, CA	042750-00061-002217	PRONTO BIG N' TUF	103601	MODERATE	A 47 year old male was exposed to product and symptoms (dizziness, vertigo, coughing, choking) started that evening. The product was sprayed into ground, he then shoveled the dirt and may have inhaled dust and also had dermal exposure
024371 - 00001	7/13/2012	IL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states a family member has been sick for about a week with breathing problems. He has been to the hospital and had prednisone and other drugs prescribed without improvement. COPD was diagnosed. The man has had some breathing issues in the past, but his symptoms got worse suddenly and quickly. About a week or two ago, the man accidentally got an unknown concentrate Roundup, diluted for use, on his skin. It splashed over the front of him and his face. He took a shower immediately. His symptoms began about one week later. No known cough or choke at the time and no other symptoms noted at the time of the exposure.
024372 - 00001	7/10/2012	TN	000524-00529	ROUNDUP PRO CONCENTRATE HERBICIDE	103601	MODERATE	Man calling with a concern about a Roundup exposure. About 2 months ago, he sprayed a 2% water dilution of Roundup Pro Concentrate and then was lying on the ground, possibly in the area just sprayed. Shortly after this exposure, the man reports he developed joint and muscle pain enough to warrant going to the doctor.
024486 - 00008	2/5/2009	ST. GABRIEL, LA		ROUNDUP	103601	MAJOR	Exposure to "Roundup" in her employment at Syngenta in St. Gabriel, LA. Child was allegedly born with defects that include developmental and respiratory abnormalities. Date of birth is

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							unknown.
024486 - 00011	8/23/2012	LA	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Woman calling is concerned that her next door neighbor is overusing Roundup used in quantity. She noticed this summer that after he sprays she has an expiratory wheeze. She went to her doctor who prescribed an inhaler that helps. She did not do the spraying nor did she feel any spray mist on her skin when she was out working in her garden when he was spraying. MRPC discussed the product toxicity. The symptom does not correlate with the expected response to the product.
024486 - 00012	8/27/2012	KY	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Man calls with concerns about his neighbor's crop spraying applied liberally by a tractor 4 months ago. He was outside during some of the application exposed because the rpm's were increased on the tractor vaporizing the Roundup making it difficult to avoid exposure. The caller states the neighbor did it on purpose. The caller thinks they used Roundup but the state testing has been inconclusive and was covered up. A state lawyer was involved. He states he feels ~c o'(became sick shortly after starting with constipation, liver problems, sinus infection, gum infection, boils, lost two teeth, woke up with his bones separated in his foot shortly after the spraying. He went to the doctor who felt his back and dental issues are the cause of the problems. The farmer told the state inspectors that Roundup was used. The caller states since he worked with the pipeline in the 1950s and 1960s he probably mixed some other chemicals with it. The man would like to know if there are any antidotes for Roundup poisoning. MRPC discussed the product toxicity. The symptoms are not related to the expected response to the product. Advised to remain under the care of MD.
024486 - 00013	8/29/2012	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	MD calling from the emergency department about a child who spent the day supervised by parents and most of that time was on an ATV. Parents were working on the farm and moving cows. Parents were also spraying weeds with 2,4-D and Roundup.

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							Child did not have any direct contact with the herbicides. Child had unpasteurized milk for the first time as well today. No witnessed ingestions of any plant material and no meds/drugs available. Child presents with a dry mouth, agitation, delirium, nystagmus, HR 150 ST, minor hyperthermia, flushed appearance. MRPC discussed the product toxicity. The symptoms do not correlate with the expected response to the product. Continue with symptomatic care and further history of possible exposure to other substances or medications.
024494 - 00019	8/13/2012	WA	071995-00007-000239	ORTHO TOTAL KILL WEED & GARDEN KILLER CONCENTRATE HERBICIDE	103601	MODERATE	Caller is a physician assistant. He has a patient who was exposed to this product about 40 minutes ago. He complains of pain. Caller reports ocular irritation. He flushed his eyes for only 10 minutes prior to presentation. At this time, P. K., a male patient, is having his eyes flushed again for a longer period of time. Caller has not done a slit lamp exam on this patient yet. After flushing, he will do that and refer to ophthalmology as needed. His eye was irrigated. No damage seen on slit lamp exam. He was prescribed an antibiotic drop. Was then released and comfortable at discharge.
024551 - 00001	9/13/2012	DE	071995-00017	ROUNDUP CONCENTRATE WEED AND GRASS KILLER 1	103601	MODERATE	Caller states she was outside, when her nephew was spraying Roundup, an 18% formulation, that had been diluted. She was near the area being treated when she felt like her throat was closing up. The caller states she is chemically sensitive. About 1.5 weeks later, she noted her eye and the side of her face along her hair line looked scalded. Her eye lid was red and puffy. It would then flake and peel. She had some ocular redness and swelling that has seemed to resolve. She was seen by her PMD and treated with oral steroids. The symptoms resolved but have come back. Now, she is being managed by an ophthalmologist and has been diagnosed with blephritis. She is currently on minocycline orally, but had previously used tobradex to the eye and eyelid. The caller suspects a relationship with the Roundup and wondering

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							what treatment should be considered.
024691 - 00001	8/2/2012	JASPER, AL	001381-00192	CORNERSTONE PLUS	103601	MODERATE	A male farm worker unintentionally drank some Cornerstone Plus that was in a water cooler. He experienced bloody diarrhea and was diagnosed with colitis.
024948 - 00001	1/3/2013	OH	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	The caller wants to know if it is possible for a person to harm himself with Roundup concentrate. Someone has drank some and is unconscious. The caller wants to know if it is possible that Roundup concentrate is the cause.
025087 - 00001	3/19/2013	CO	000524-00445	ROUNDUP HERBICIDE	103601	MAJOR	Monsanto/Scott company calling about an older female who has sent an e-mail or letter to the company claiming exposure to Roundup Concentrate has caused Parkinson's disease. The woman stated that her exposure was "dipping her hands in a Roundup solution."
025157 - 00001	4/25/2013	OH	000524-00445	ROUNDUP HERBICIDE	103601	DEATH,MAJOR	An adult female emailed about a study she read on tumors in rats exposed to Roundup. Her husband & a neighbor both died of tumors. She and husband were exposed to Roundup 3 years ago and both developed tumors. She is concerned about her own health. She provided no phone number. Monsanto emailed a response and asked her to contact them but she didn't. Exposure to Roundup is not clear.
025228 - 00001	4/14/2013	CA	000524-00517	RANGER PRO	103601	MODERATE	Caller states that about 30 minutes ago she poured some Ranger Pro Herbicide into a measuring cup for her husband to dilute the product. She started to feel weird and to wheeze. Caller states that more than 20 years ago, she was spraying a Wilson Leather Protectant product and inhaled some resulting in 70% lung capacity and now she seems to be very sensitive to chemical smells. She went inside and used her inhaler and is feeling better.
025233 - 00001	4/26/2013	ID	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states he has just put all the pieces of this together, and before he sees a doctor he wants information. He states someone sneaked in during the middle of the night several months ago and poisoned his apricot tree and other trees. He then ate the apricots. He thinks it was a neighbor lady, who has passed away now, but he saw a Roundup container at her house before she departed. He has

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							symptoms of weakness in his lower extremities and numbness to his feet and legs.
025234 - 00001	4/19/2013	GA	042750-00061	GLY STAR PLUS FROM AGRI STAR	103601	MODERATE	Caller states that about a month ago he was using Gly Star Plus and got some of the concentrate on his hands. He rinsed it off right away but then realized the concentrate had been on the handle of the sprayer he was using. Two days after the exposure, he had flu like symptoms, profuse watery diarrhea, nausea, vomiting, and abdominal pain. He now has periods of itching all over and small red bumps noted on his chest. When he sits down and then gets up he gets chills up and down his legs. He has not seen a doctor for his symptoms yet.
025309 - 00001	2/1/2013	KY	071995-00023	ROUNDUP WEED AND GRASS KILLER1 READY TO USE	103601	MODERATE	Caller states she used a ready to use Roundup 3 months ago while wearing shorts. She assumes some of the mist got on her legs. She did not shower afterwards. Two days later, she developed a rash that looked "like bites" or tiny bumps on the front of her legs. She went to her primary MD who gave her an antibiotic and steroid combination cream. She used it, and the rash faded but came right back. It is very pruritic. She went to one dermatologist that she feels was just "guessing" about the rash and has an appointment for next Wednesday with another dermatologist. The caller states she has used Roundup for years and never had a problem until this time.
025312 - 00001	5/1/2013	FL	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that 4 weeks ago, she was riding a cart at a golf course when she got covered with the spray of a Roundup product from a truck that was in front of her. The caller says that she must have inhaled the Roundup, because she has had a cough since that time. Occasionally mucous comes up with the cough. In speaking with the caller, the cough is intermittent. A few times a day she has had a runny nose that pre-dates the exposure. The woman has not sought any evaluation or treatment by a MD.
025314 - 00001	5/14/2013	MO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that she was exposed to Roundup earlier today around noon time, and is now "very sick". She states that her neighbor sprayed

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							Roundup in her yard to try to kill her. The neighbor told her that she was "a weed that needed to be gotten rid of'. The caller states she inhaled some of the product when she was in her yard as he was spraying it. She thinks her neighbor was using one of the concentrated products, but is not sure exactly which one. The caller complains of throat irritation, palpitations, trouble breathing, and "very sharp" chest pain. On follow up, the woman was observed and monitored for several hours and had been discharged to home.
025315 - 00001	5/22/2013	IN	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Caller states that last week her husband used a weed killer. There are three different weed killers in their garage, she is unsure of which product he used. The caller states that her husband is hospitalized with an infection and 2 blood clots in his leg and is concerned that this could be caused by Roundup getting into a cut that he had on his arm while using the weed killer. Unknown the type of infection or if the infection is in his arm wound. He is currently receiving antibiotic therapy.
025316 - 00001	5/26/2013	CO	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Man used an unspecified formula of diluted Roundup concentrate for about 2 hours. There was a little wind on that day. He got some on his hands as he mixed it. No accidents during spraying. Denies working with any poison ivy/oak. He showered with soap and water within an hour of finishing his spraying. He has not used Roundup before. No new soaps or foods. The only thing different over the last 3 days is, he has been using his Ventolin HFA inhaler that he was prescribed during a bout with pneumonia this past year. No difficulty breathing or wheezing is reported. The Roundup was mixed 6 ounces to 2 gallons of water. The next day, a raised itchy rash started on bilateral arms, worse on forearms, some on top of hands, on both ankles above his socks, and neck. All these areas of skin were exposed during the use of the product. He has started using topical hydrocortisone cream. On follow up, the man stated after he took a dose

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							of the Benadryl, his itching had resolved and he was feeling well and going back outside to do more yard work. On further follow up, the man said later that evening, he went to the ER for worsening of symptoms. He was advised by the MD to continue taking Benadryl, and was prescribed prednisone and Pepcid. The hives and itching were clearing. He was diagnosed with Urticaria/hives secondary to environmental allergies.
025347 - 00005	3/6/2013	CA		ROUND UP CONCENTRATE	103601	MODERATE	An individual has been hospitalized after drinking Round Up (active ingredient: Glyphosate).The patient stated that he accidently ingested the Round Up Concentrate that was stored in the garage. The patient had purchased the Round Up Concentrate at Home Depot about a month ago and after use stored the remaining pesticide in a V-8 Juice bottle in the garage. He drank out of the V-8 bottle thinking it was juice. Once he realized what he drank was not V-8 Juice, he rinsed his mouth with water and mouthwash but did not tell anyone what had happen since he did not feel any symptoms. At about 7 pm the same day, he began to feel ill with throat pain and told his wife what had happened that morning. The wife transported him to the Kaiser Permanente hospital where he was admitted for treatment.
025424 - 00001	6/17/2013	TX	000524-00445	ROUNDUP HERBICIDE	103601	MODERATE	Adult female calling about possibly pulling weeds on that her husband had sprayed with Roundup the day before. Her hands were red the evening after pulling the weeds. The next day, her hands were swollen and she developed hives everywhere. She went to the ER and was given steroids and was better. Today, she went back to the ER because of difficulty breathing.
025583 - 00005	7/1/2013	NJ	000524-00445	ROUNDUP	103601	MODERATE	Neighbor sprayed caller's property sometime before the weekend getting an unknown formulation of Roundup on her fig trees. The leaves on the fig are not withered but are not as robust as usual. Family members enjoy the fruit,

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							peeling it before eating. On Saturday, the caller, her adult son, his friend and his friends 6 month pregnant wife helped her cut down the fig tree and carry the plant branches to a dumpster. Of all the 4 people who cleared the fig tree the son's male friend (who is allergic to everything) had bronchospasms for which he needed a breathing treatment in an ER. He was discharged to home and is fine now. It is unconfirmed whether Roundup was actually on the fig tree.
025583 - 00006	7/19/2013	FL	000524-00445	ROUNDUP	103601	MODERATE	Caller states that her neighbor was using a diluted Roundup product in her own sprayer. Something happened with the hose and she ended up getting diluted Roundup into her eye about 20 minutes ago. Prior to calling, she did attempt to irrigate her eye using an eye cup. Her eye is still burning and stinging. On follow up, the woman stated she had a foreign body sensation. She was referred to her ophthalmologist for an eye exam and treatment. She was diagnosed with a corneal burn to the corner of her eye. She was prescribed antibiotic and steroid drops and is scheduled to follow up with the ophthalmologist.
025583 - 00008	7/31/2013	CA	071995-00025	ROUNDUP WEED AND GRASS KILLER SUPER CONCENTRATE	103601	MODERATE	Woman calling regarding herself, stating she has been having "stomach issues" and works with Roundup frequently. She says that she has accidentally drunk some diluted Roundup but her signs and symptoms have been going on for about 3 months now. Caller says that the "cancer meds" she is taking could also be the cause of her symptoms.
025583 - 00009	7/17/2013	IL	071995-00023	ROUNDUP WEED AND GRASS KILLER1 READY TO USE	103601	MODERATE	Caller states 7 4 year old male in good health, was picking weeds, 1 year ago, from a garden not knowing his wife had sprayed with Roundup Ready to Use. He was not wearing gloves but washed his hands after pulling the weeds. Since then, he has had an itching rash on the inside palm of his right hand. It feels tender and is sensitive to touch. "Cold water will irritate". He has been to a few dermatologists and has taken corticosteroids. Recently, he was given Flucanozole in case it is a

Incident Package Report	Incident Date	Location	Reg Number	Product Name	PC Code	Exposure Severity	Incident Description
							fungus infection
025583 - 00011	7/1/2012	NJ	000524-00475	ROUNDUP ULTRA	103601	MAJOR	A nurse in New Jersey asked to speak with someone about Roundup Ultra and a strange illness her brother-in-law has had for a year now. She stated that he has a farm and used Roundup Ultra and doctors cannot find anything wrong with him but to say his body may have had an allergic reaction from using the Roundup product. His blood work shows nothing but his body has been swollen and she fears he doesn't have much time left.

Appendix 3

SENSOR-Pesticides 1998-2009 Moderate & High Severity Glyphosate Cases			
Case ID	Year	Severity	Case Description
CA15534	2008	High	Roundup drifted onto officer as he was responding to an accident on the side of the freeway
FL02294	2007	High	45 y/o man was spraying product and hose started leaking and product spilled on both hands. Did not wash immediately.
FL02346	2007	High	Male has been using high yield zawl for almost a month.
FL03304	2009	High	Patient is suspected of trying to commit suicide by ingesting an unknown amount of roundup weed and grass killer concentrate
LA00205	2001	High	mother bought pest. from man in neighborhood; stored in v8 container; mentally ill brother used pest. to make choc. milk
NC01758	2009	High	Man ingested roundup from an antifreeze bottle with beer or wine Caller is EMS has man who has ingested 8-16 oz of Roundup from an antifreeze container and alcohol. He has symptoms of vomiting several times, hypotension, blood pressure drop, acidotic, respiratory arrest apnea, has developed wide complex tachycardia. His prior medical history is negative.
CA02204	1998	Moderate	Not Available
CA03535	1998	Moderate	Not Available
CA03640	1998	Moderate	Not Available
CA03704	1998	Moderate	Not Available
CA04445	1999	Moderate	Not Available
CA05234	1999	Moderate	Not Available
CA05260	1998	Moderate	Not Available
CA05563	1999	Moderate	Not Available
CA06363	1999	Moderate	Not Available
CA07993	2000	Moderate	Not Available
CA09242	2001	Moderate	Not Available
CA09383	2001	Moderate	Not Available
CA09779	2001	Moderate	Not Available
CA10137	2002	Moderate	Not Available
CA11225	2002	Moderate	Not Available
CA13383	2003	Moderate	Not Available
CA13488	2003	Moderate	Not Available
CA14027	2004	Moderate	He used a new weed spray and broke out in rashes the next morning
CA14187	2002	Moderate	Works spraying chemicals, now has a rash
CA14302	2005	Moderate	Round-up got in both eyes
CA14626	2006	Moderate	Developed red burning marks and blisters on his chest, back, and arm after using chemicals at work.
CA15535	2008	Moderate	Wearing a backpack sprayer and it leaked

SENSOR-Pesticides 1998-2009 Moderate & High Severity Glyphosate Cases			
Case ID	Year	Severity	Case Description
CA15626	2008	Moderate	Hose malfunctioned and leather gloves were soaked with glyphosate
CA15644	2008	Moderate	The hose of a sprayer broke and splashed his face/eyes
CA15707	2008	Moderate	Confused, mixed roundup with soda and drank it
CA15957	2008	Moderate	Backpack sprayer leaked
FL00379	1998	Moderate	While applying glyphosate, complainant cut her arm on a tree branch. The chemical irritated and burned the cut tissue.
FL00621	1999	Moderate	Dockworker alleges pesticide drifted onto him after a pesticide application. He was neck deep in water at the time.
FL01328	2004	Moderate	Neighbor applied pesticide at fence line. Residents were exposed and got ill.
FL01531	2006	Moderate	26y/o male admits to ing approx 8oz of Round up concentrate plus weed/grass killer
FL01588	2006	Moderate	Patient worked with chemical for a few days at high levels. Not wearing protective gear.
FL01671	2006	Moderate	Patient was exposed to open container of round-up at work
FL01930	2006	Moderate	Patient was spraying round up in his yard and got some in his eyes.
FL02292	2007	Moderate	9 year old was sprayed in eye by a herbicide.
FL02375	2007	Moderate	Landscaper was exposed to glyphosate to days ago.
FL02521	2007	Moderate	Male was working on yard and spraying product. Some product got on hands.
FL03631	2009	Moderate	Not Available
LA00998	2003	Moderate	Drift from aerial application to sugar cane field behind home. Plane was spraying Polado herbicide (glyphosate) Walking in yard and noticed an aerial application to sugar cane field behind home. SX of headache, SOB, eye irritation, and abdominal pain. Complainant called sheriff and was taken to ER for treatment.
LA01692	2005	Moderate	Got round up in eyes at work; cleaning tank; backsplash into face and eyes
LA02721	2007	Moderate	mixed (clorox + roundup concentrate plus weed and grass killer)then spilled on arm; dermal irritation
LA03061	2008	Moderate	child at aunt's house yesterday was sprayed in face with (maxide ready-to-use grass and weed killer)
MI00036	2001	Moderate	working in field, spraying roundup, when wind shifted. Sprayed on field, unknown type of sprayer.

SENSOR-Pesticides 1998-2009 Moderate & High Severity Glyphosate Cases			
Case ID	Year	Severity	Case Description
MI00276	2003	Moderate	Mixture of pesticides spilled in storage room. He has history of industrial asthma & when he walked by, could not breathe.
MI00397	2005	Moderate	Farm exposure to mixture of roundup, ammonium sulfate, & liquid nitrogen. Flushed eyes & arm before going to ED.
MI00583	2005	Moderate	Was trying to unclog pump, got some spray in her eye. Rinsed with hose at work.
MI01980	2009	Moderate	Not Available
NC00086	2007	Moderate	Woman purposefully ingested Roundup at home. 30 year old woman intentionally ingested Roundup Brushkiller Concentrate on 04/19/2007. Somebody from her house called Poison Control. The patient started vomiting and had a strong abdominal pain. She was taken to a nearby hospital and was admitted to the critical care unit. According to surveillance program records, the patient was still in hospital on 04/20/2007 but her condition was improved.
NY00313	2000	Moderate	Woman was working in her garden using a pump bottle of ready-to-use Roundup herbicide. Woman was working in her garden using a pump bottle of ready to use Roundup Lawn & Grass herbicide. She did not follow instructions & was not wearing protective clothing, eye wear or gloves. She states that she was sprayed as there was a drift wind and also she states that the trigger pump was leaking down her hand & wrist.
OR01583	2007	Moderate	Splashed glyphosate in both eyes after turning on high-pressure hose.
TX01850	2000	Moderate	Case is a farmworker/licensed pesticide applicator and had been spraying round-up near cotton fields for approximately 2 week
TX02115	2000	Moderate	Case mixes and applies round-up daily as part of job on ranch. Wears no protection and contact is common. Developed painful
TX04618	2005	Moderate	Case was putting bottle of roundup on top shelf, bottle fell over splashing case in face & eyes.
TX05736	2008	Moderate	case exposed to herbicide at work while spraying weeds and brush along a city road; wind caused spray to blow back at him.
WA00936	2002	Moderate	40 y/o female employee of Walmart reported a skin rash/irritation following contact with a herbicide. She was stocking the shelves when exposed. About 9 days later she sought medical attention.
WA01571	2004	Moderate	A 43 y/o female was applying an herbicide and was sprayed in the right eye from a cracked nozzle assembly. She washed with running water for 10-15 minutes and still developed ocular pain. She sought medical attention the same day.
WA02644	2007	Moderate	A 21 y/o male landscaper worker, according to medical records, inhaled fumes while spraying plants. He developed symptoms and presented at clinic with respiratory, G.I., cardiovascular, neurological and dermal symptoms one day after exposure. He was treated and released, returning again to clinic next day. Patient was lost to follow-up and employer did not supply spray records as requested.

SENSOR-Pesticides 1998-2009 Moderate & High Severity Glyphosate Cases			
Case ID	Year	Severity	Case Description
WA03234	2009	Moderate	A 40 y/o male tractor driver developed respiratory symptoms and eye irritation after he drove the tractor disking soil in the vineyard behind a boom sprayer applying herbicide. The tractor driver wore a face mask. He went to the emergency department and continued to seek medical care afterwards for asthma-like symptoms. He had a history of environmental allergies but no prior history of asthma. The herbicide was applied to the vineyard eleven times over a 5-week period.

Appendix 4

Glyphosate: Literature Review Methodology

To identify the epidemiological investigations of the association between glyphosate exposure and adverse health effects, we queried PubMed/Medline and the Institute of Scientific Information's Web of Science. We also performed limited searches using Google.Scholar. Querying these three search engines is considered a comprehensive way to identify relevant articles (Falagas, 2008). PubMed is the most commonly used biomedical search engine used by researchers today, however Web of Science offers similar journal coverage in addition to citation mapping capabilities. We performed citation mapping using Web of Science, examining key articles which referenced the articles included in the literature review, to identify additional relevant material. We also sought relevant articles through Googel.Scholar. These methods are discussed herein.

We generated the following search strings. Emphasis was placed upon identification of all possible epidemiological studies available, and the ability to use the identical search string in both PubMed/Medline and Web of Science. Regarding Google.Scholar, we attempted use of similar search strings as well as the advanced search capabilities available [http://scholar.google.com/advanced_scholar_search?hl=en&as_sdt=20000].
The search strings are found below:

> PubMed: (((Glyphosate[tw] OR (N-(phosphonomethyl)glycine[tw]) OR gliphosate[tw] OR Roundup[tw] OR yerbimat[tw] OR (glyphosate hydrochloride (2:1)[tw]) AND (humans[tw] AND (epidemiologic studies[tw] OR cohort*[tw] OR case control[tw] OR cross section*[tw] OR cluster*[tw] OR environmental exposure*[tw] OR occupational exposure*[tw] OR ecologic stud*[tw] OR aggregate stud*[tw])))
> Web of Science: ((((Glyphosate OR (N-(phosphonomethyl)glycine) OR gliphosate OR Roundup OR yerbimat OR (glyphosate hydrochloride (2:1))) AND human AND (epidemiologic stud* OR cohort* OR case control OR cross section* OR cluster* OR environmental exposure* OR occupational exposure* OR ecologic stud* OR aggregate stud*))))

We did not restrict the date of publication; however with a few exceptions most studies identified were published 1990-present. After elimination of duplicate references between the two search engines, we identified 90 research articles of potential interest. For inclusion in this review, articles were published in English language, analytic epidemiologic investigation, and included a glyphosate risk estimate. Among the 59 articles excluded from review at this point in the search process, 12 were evaluation of human exposure only, 16 related to an acute pesticide poisoning incident(s), 8 articles concerned evaluation of ecological exposure (non-human) only, 7 were experimental toxicological studies and 6 were review articles or editorials (not original research) or did not meet inclusion criteria for other reasons. Therefore, there were 31 full-text original epidemiological research articles of an association between glyphosate exposure and an adverse human health outcomes included in full-text review, and 10 were included in the HED review. There were 21 articles excluded as a result of full-text review (14 exposure-only, no epidemiological risk assessment; 6 review articles; and 1 toxicological study).

Citation mapping included review of two high-quality summary articles of the investigation into glyphosate toxicity in the human population (Mink et al., 2011; Pamela J. Mink, Jack S. Mandel, Bonnielin K. Sceurman, & Jessica I. Lundin, 2012), and use of citation mapping tools in PubMed and Web of Science. Through these methods, we identified an additional 40 unique epidemiology articles (36 from the Mink et al reviews, and 4 using mapping techniques). Mink et al. included all studies in which a glyphosate risk estimate was measured, whether or not glyphosate was an *a priori* hypothesis, and regardless of the direction of the point estimate, *i.e.*, all null studies were included. In addition, HED reviewed the recently released European Food Safety Authority (EFSA) pesticide epidemiology systematic review (with searchable Excel spreadsheet) and identified an additional 5 epidemiology studies. Therefore, there were 55 studies included in this review (10 from the original search, 40 from citation mapping including evaluation of review article reference lists, and 5 from the EFSA systematic review).

Targeted searching using Google Scholar identified additional 63 unique articles using the following search string (Date searched 11/20/13):

> Google Scholar: [glyphosate epidemiology cohort OR "case control" OR "cross sectional" "human health risk"]

Because Google Scholar search tools are more limited than Medline or Web of Science, the original search could not limit to only articles of original research published in scholarly peer-reviewed journals, *i.e.*, news articles, commentary and reviews or editorials were initially identified. However, review of the 63 Google Scholar "hits" did not identify any additional original articles, not previously identified.

Upon completion of this process, we identified a total of 55 full text articles for inclusion. Attached appendices include a delineation of all references originally captured with the stated search string in both PubMed and Web of Science, and the final listing of included and excluded articles.

	Reference:	Included? (yes/no)
1	Abass, K., Turpeinen, M., & Pelkonen, O. (2009). An evaluation of the cytochrome P450 inhibition potential of selected pesticides in human hepatic microsomes. *Journal of Environmental Science and Health Part B-Pesticides Food Contaminants and Agricultural Wastes, 44*(6), 553-563. doi: 10.1080/03601230902997766	NO
2	Acquavella, J. F., Alexander, B. H., Mandel, J. S., Burns, C. J., & Gustin, C. (2006). Exposure misclassification in studies of agricultural pesticides: insights from biomonitoring. *Epidemiology, 17*(1), 69-74.	NO
3	Acquavella, J. F., Alexander, B. H., Mandel, J. S., Gustin, C., Baker, B., Chapman, P., & Bleeke, M. (2004). Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. *Environ Health Perspect, 112*(3), 321-326.	NO
4	Acquavella, J. F., Weber, J. A., Cullen, M. R., Cruz, O. A., Martens, M. A., Holden, L. R., . . . Farmer, D. (1999). Human ocular effects from self-reported exposures to Roundup (R) herbicides. *Human & Experimental Toxicology, 18*(8), 479-486. doi: 10.1191/096032799678847087	NO
5	Acquavella, J., Farmer, D., & Cullen, M. R. (1999). A case-control study of Non-Hodgkin lymphoma and exposure to pesticides Cancer (Vol. 86, pp. 729-731). United states.	NO
6	Adomas, B., Antczak-Marecka, J., Nalecz-Jawecki, G., & Piotrowicz-Cieslak, A. I. (2013). Phytotoxicity of Enrofloxacin Soil Pollutant to Narrow-Leaved Lupin Plant. *Polish Journal of Environmental Studies, 22*(1), 71-76.	NO
7	Alavanja, M. C., Dosemeci, M., Samanic, C., Lubin, J., Lynch, C. F., Knott, C., Blair, A. (2004). Pesticides and lung cancer risk in the agricultural health study cohort. Am J Epidemiol, 160(9), 876-885. doi: 160/9/876 [pii]	YES
8	Alavanja, M. C., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C. F., . . . Blair, A. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *Am J Epidemiol, 157*(9), 800-814.	YES

9	Andreotti, G., Freeman, L. E., Hou, L., Coble, J., Rusiecki, J., Hoppin, J. A., Alavanja, M. C. (2009). Agricultural pesticide use and pancreatic cancer risk in the Agricultural Health Study Cohort. *Int J Cancer, 124*(10), 2495-2500. doi: 10.1002/ijc.24185	YES
10	Arbuckle, T. E., Lin, Z. Q., & Mery, L. S. (2001). An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environmental Health Perspectives, 109*(8), 851-857. doi: 10.2307/3454830	YES
11	Astiz, M., de Alaniz, M. J. T., & Marra, C. A. (2009). Effect of pesticides on cell survival in liver and brain rat tissues. *Ecotoxicology and Environmental Safety, 72*(7), 2025-2032. doi: 10.1016/j.ecoenv.2009.05.001	NO
12	Baker, B. A., Alexander, B. H., Mandel, J. S., Acquavella, J. F., Honeycutt, R., & Chapman, P. (2005). Farm Family Exposure Study: methods and recruitment practices for a biomonitoring study of pesticide exposure. *J Expo Anal Environ Epidemiol, 15*(6), 491-499. doi: 10.1038/sj.jea.7500427	NO
13	Band, P. R., Abanto, Z., Bert, J., Lang, B., Fang, R., Gallagher, R. P., & Le, N. D. (2011). Prostate Cancer Risk and Exposure to Pesticides in British Columbia Farmers. *Prostate, 71*(2), 168-183. doi: 10.1002/pros.21232	YES
14	Bolognesi, C., Carrasquilla, G., Volpi, S., Solomon, K. R., & Marshall, E. J. P. (2009). Biomonitoring of GeNOtoxic Risk in Agricultural Workers from Five Colombian Regions: Association to Occupational Exposure to Glyphosate. Journal of Toxicology and Environmental Health-Part a-Current Issues, 72(15-16), 986-997. doi: 10.1080/15287390902929741	NO
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106	Pedroso, J. A., & Silva, C. A. (2010). The nephrologist as a consultant for acute poisoning: epidemiology of severe poisonings in the State of Rio Grande do Sul and techniques to enhance renal elimination. *J Bras Nefrol, 32*(4), 340-348.	NO

107	Peterson, R. K. D., & Shama, L. M. (2005). A comparative risk assessment of genetically engineered, mutagenic, and conventional wheat production systems. *Transgenic Research, 14*(6), 859-875. doi: 10.1007/s11248-005-1411-8	NO
108	Potti, A., & Sehgal, I. (2005). Exposure to pesticides increases levels of uPA and uPAR in pre-malignant human prostate cells. *Environmental Toxicology and Pharmacology, 19*(2), 215-219. doi: 10.1016/j.etap.2004.04.010	NO
109	Ruder, A. M., Waters, M. A., Butler, M. A., Carreón, T., Calvert, G. M., Davis-King, K. E., Group, B. C. C. S. (2004). Gliomas and farm pesticide exposure in men: the upper midwest health study. *Arch Environ Health, 59*(12), 650-657.	YES
110	Rull, R. P., Ritz, B., & Shaw, G. M. (2006). Neural tube defects and maternal residential proximity to agricultural pesticide applications. *American Journal of Epidemiology, 163*(8), 743-753. doi: 10.1093/aje/kwj101	YES
111	Saldana, T. M., Basso, O., Hoppin, J. A., Baird, D. D., KNOtt, C., Blair, A., . . . Sandler, D. P. (2007). Pesticide exposure and self-reported gestational diabetes mellitus in the agricultural health study. Diabetes Care, 30(3), 529-534. doi: 10.2337/dc06-1832	YES
112	Sanin, L. H., Carrasquilla, G., Solomon, K. R., Cole, D. C., & Marshall, E. J. (2009). Regional differences in time to pregnancy among fertile women from five Colombian regions with different use of glyphosate. *J Toxicol Environ Health A, 72*(15-16), 949-960. doi: 10.1080/15287390902929691	YES
113	Sathyanarayana, S., Basso, O., Karr, C., LozaNO, P., Alavanja, M., Sandler, D., & Hoppin, J. (2010). Maternal Pesticide Use and Birth Weight in the Agricultural Health Study. Journal of Agromedicine, 15(2), 127-136. doi: 10.1080/10599241003622699	YES
114	Savitz, D. A., Arbuckle, T., Kaczor, D., & Curtis, K. M. (1997). Male pesticide exposure and pregnancy outcome. *Am J Epidemiol, 146*(12), 1025-1036.	YES
115	Schilmann, A., Lacasana, M., Blanco-MuNOz, J., Aguilar-GarduNO, C., Salinas-Rodriguez, A., Flores-Aldana, M., & Cebrian, M. E. (2010). Identifying pesticide use patterns among flower growers to assess occupational exposure to mixtures. Occup Environ Med, 67(5), 323-329. doi: 10.1136/oem.2009.047175	NO

116	Semal, J. (2007). Patentability of living organisms: From biopatent to bio-big-bang. *Cahiers Agricultures, 16*(1), 41-48.	NO
117	Senior, I. J., & Dale, P. J. (2002). Herbicide-tolerant crops in agriculture: oilseed rape as a case study. *Plant Breeding, 121*(2), 97-107. doi: 10.1046/j.1439-0523.2002.00688.x	NO
118	Settimi, L., Davanzo, F., Travaglia, A., Locatelli, C., Cilento, I., Volpe, C., Urbani, E. (2007). [Italian Program for Surveillance of Acute Pesticide-Related Illnesses: cases identified in 2005]. *G Ital Med Lav Ergon, 29*(3 Suppl), 264-266.	NO
119	Shi, G., Peng, M. C., & Jiang, T. (2011). MultiMSOAR 2.0: an accurate tool to identify ortholog groups among multiple geNOmes. PLoS One, 6(6), e20892. doi: 10.1371/journal.pone.0020892	NO
120	Slager, R. E., Poole, J. A., LeVan, T. D., Sandler, D. P., Alavanja, M. C., & Hoppin, J. A. (2009). Rhinitis associated with pesticide exposure among commercial pesticide applicators in the Agricultural Health Study. *Occup Environ Med, 66*(11), 718-724. doi: 10.1136/oem.2008.041798	YES
121	Slager, R. E., Simpson, S. L., Levan, T. D., Poole, J. A., Sandler, D. P., & Hoppin, J. A. (2010). Rhinitis associated with pesticide use among private pesticide applicators in the agricultural health study. *J Toxicol Environ Health A, 73*(20), 1382-1393. doi: 10.1080/15287394.2010.497443	YES
122	Smart, T., & Torres, G. (1996). Antiviral roundup. *GMHC Treat Issues, 10*(8), 6-7.	NO
123	Solomon, K. R., Anadon, A., Carrasquilla, G., Cerdeira, A. L., Marshall, J., & Sanin, L. H. (2007). Coca and poppy eradication in Colombia: environmental and human health assessment of aerially applied glyphosate. *Rev Environ Contam Toxicol, 190*, 43-125.	NO
124	Solomon, K. R., Marshall, E. J. P., & Carrasquilla, G. (2009). Human Health and Environmental Risks from the Use of Glyphosate Formulations to Control the Production of Coca in Colombia: Overview and Conclusions. *Journal of Toxicology and Environmental Health-Part a-Current Issues, 72*(15-16), 914-920. doi: 10.1080/15287390902929659	NO
125	Sowers, V. (1992). Healthcare uniform service market poised for expansion. *Text Rent, 75*(9), 38, 40, 42-34.	NO

126	Valcin, M., Henneberger, P. K., Kullman, G. J., Umbach, D. M., London, S. J., Alavanja, M. C. R., Hoppin, J. A. (2007). Chronic bronchitis among NOnsmoking farm women in the agricultural health study. Journal of Occupational and Environmental Medicine, 49(5), 574-583. doi: 10.1097/JOM.0b013e3180577768	YES
127	van Haver, E., Alink, G., Barlow, S., Cockburn, A., Flachowsky, G., Knudsen, I., Williams, A. (2008). Safety and nutritional assessment of GM plants and derived food and feed: The role of animal feeding trials. *Food and Chemical Toxicology, 46*, S2-S70. doi: 10.1016/j.fct.2008.02.008	NO
128	Varona, M., Lucia Henao, G., Diaz, S., Lancheros, A., Murcia, A., Rodriguez, N., & Hugo Alvarez, V. (2009). Effects of aerial applications of the herbicide,glyphosate and insecticides on human health. *Biomedica, 29*(3), 456-475.	NO
129	Wang, G., Fan, X. N., Tan, Y. Y., Cheng, Q., & Chen, S. D. (2011). Parkinsonism after chronic occupational exposure to glyphosate *Parkinsonism Relat Disord* (Vol. 17, pp. 486-487). England.	NO
130	WECHSLER, L., CHECKOWAY, H., FRANKLIN, G., & COSTA, L. (1991). A PILOT-STUDY OF OCCUPATIONAL AND ENVIRONMENTAL RISK-FACTORS FOR PARKINSONS-DISEASE. *Neurotoxicology, 12*(3), 387-392.	YES
131	Wester, R. C., Melendres, J., Serranzana, S., & Maibach, H. I. (1994). Time-response necessary in validation for extraction of pesticides from cloth patches used in field exposure studies. *Arch Environ Contam Toxicol, 27*(2), 276-280.	NO
132	Williams, A. L., Watson, R. E., & DeSesso, J. M. (2012). DEVELOPMENTAL AND REPRODUCTIVE OUTCOMES IN HUMANS AND ANIMALS AFTER GLYPHOSATE EXPOSURE: A CRITICAL ANALYSIS. *Journal of Toxicology and Environmental Health-Part B-Critical Reviews, 15*(1), 39-96. doi: 10.1080/10937404.2012.632361	NO
133	Williams, G. M., Kroes, R., & Munro, I. C. (2000). Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. *Regul Toxicol Pharmacol, 31*(2 Pt 1), 117-165. doi: 10.1006/rtph.1999.1371	NO

134	Yiin JH, Ruder AM, Stewart PA, Waters MA, Carreón T, Butler MA, Calvert GM, Davis-King KE, Schulte PA, Mandel JS, Morton RF, Reding DJ, Rosenman KD; Brain Cancer Collaborative Study Group. The Upper Midwest Health Study: a case-control study of pesticide applicators and risk of glioma. Environ Health. 2012 Jun 12;11:39.	YES
135	Zawahir, S., Roberts, D. M., Palangasinghe, C., Mohamed, F., Eddleston, M., Dawson, A. H., Gawarammana, I. (2009). Acute intentional self-poisoning with a herbicide product containing fenoxaprop-P-ethyl, ethoxysulfuron, and isoxadifen ethyl: a prospective observational study. Clin Toxicol (Phila), 47(8), 792-797. doi: 10.1080/15563650903174810	NO

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Kent, Ray
Sent: Mon 9/28/2015 7:37:59 PM
Subject: RE: Glyphosate

Jess,

Thanks for the kudos. It's been a pleasure to work with you on this.

Ray

From: Rowland, Jess
Sent: Monday, September 28, 2015 3:31 PM
To: Kent, Ray
Subject: RE: Glyphosate

Raymond

Thank You SO MUCH for ALL your help with this CARC effort. For the secondary reviews, help at the meeting, with the documents etc.

Regards

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Kent, Ray
Sent: Monday, September 28, 2015 3:05 PM
To: Rowland, Jess
Subject: RE: Glyphosate

Jess,

Ex. 5 - Deliberative Process

Ray

From: Rowland, Jess
Sent: Sunday, September 27, 2015 9:02 PM
To: Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Dunbar, Anwar; Kent, Ray; Liccione, John; Lobdell, Danelle; Middleton, Karlyn; McCarroll, Nancy; Wood, Charles
Subject: Glyphosate
Importance: High

Greg et al.,

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Thanks for all your help; special thanks to the valuable contributions by Charles and Danelle.

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Rowland, Jess[Rowland.Jess@epa.gov]
From: Kent, Ray
Sent: Mon 9/28/2015 7:04:48 PM
Subject: RE: Glyphosate
Glyphosate CARC FINAL 9.27.15 JR -ray.docx

Jess,

Ex. 5 - Deliberative Process

Ray

From: Rowland, Jess
Sent: Sunday, September 27, 2015 9:02 PM
To: Akerman, Gregory; Brunsman, Lori; Chen, Jonathan; Dunbar, Anwar; Kent, Ray; Liccione, John; Lobdell, Danelle; Middleton, Karlyn; McCarroll, Nancy; Wood, Charles
Subject: Glyphosate
Importance: High

Greg et al.,

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Ex. 5 - Deliberative Process

Thanks for all your help; special thanks to the valuable contributions by Charles and Danelle.

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

From: Kent, Ray
Location: 10621
Importance: Normal
Subject: Accepted: Glyphosate - CARC - Continues.....
Start Date/Time: Wed 9/16/2015 5:00:00 PM
End Date/Time: Wed 9/16/2015 8:00:00 PM

From: Kent, Ray
Location: 10100
Importance: Normal
Subject: Accepted: Glyphosate - CARC
Start Date/Time: Wed 9/16/2015 1:00:00 PM
End Date/Time: Wed 9/16/2015 4:00:00 PM

To: Miller, David[Miller.DavidJ@epa.gov]
From: Kent, Ray
Sent: Mon 3/23/2015 3:33:52 PM
Subject: RE: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos/parathion)
Glyphosate 2nd peer review 1991.pdf

David, fyi…

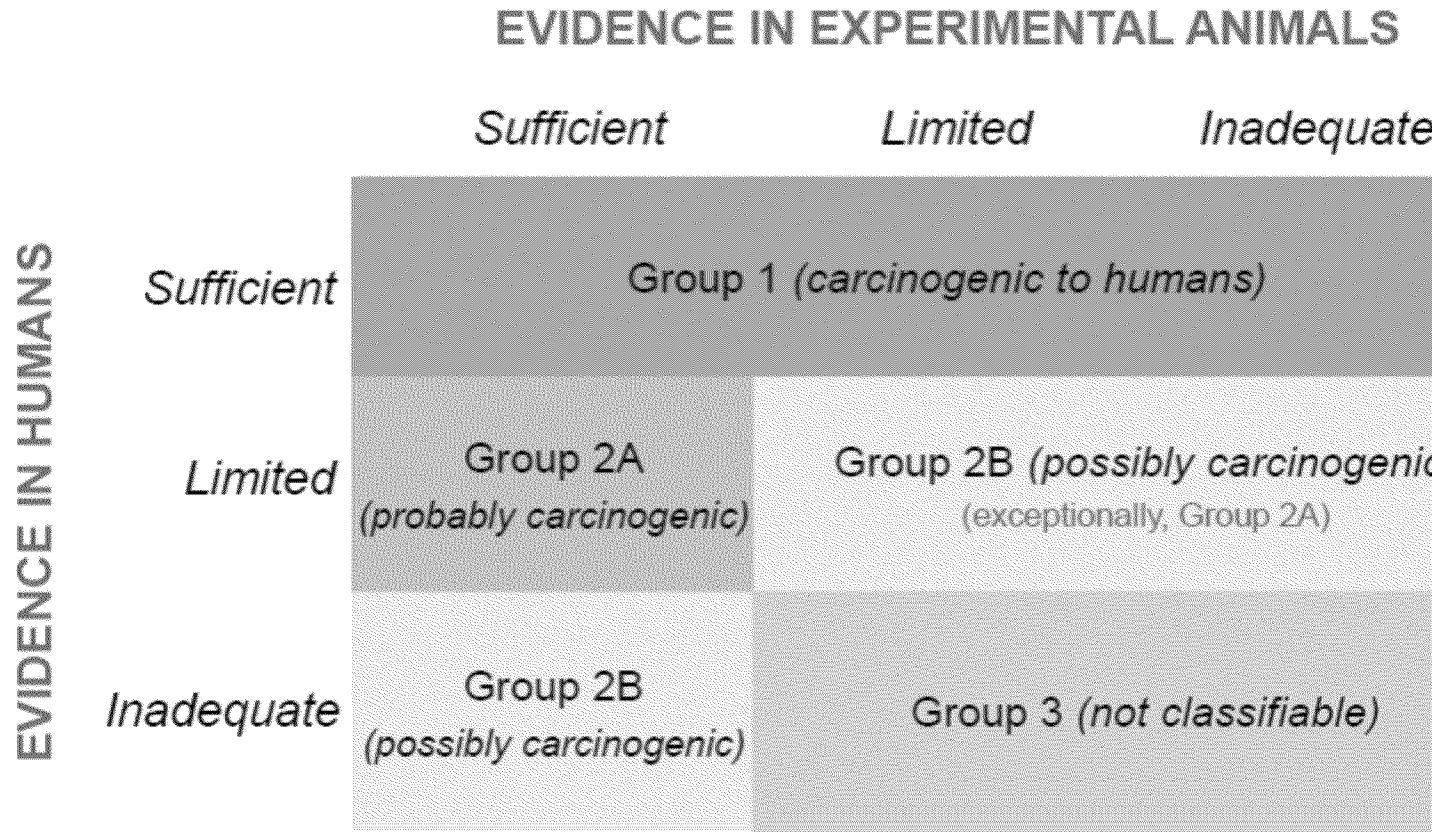
Ex. 5 - Deliberative Process

Ray

From: Miller, David
Sent: Friday, March 20, 2015 2:53 PM
To: OPP HED
Subject: FW: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos/parathion)

FYI – for those with an interest, the attached is the recently released IARC summary report on findings for malathion/diazinon/ glyphosate/ tetrachlorpvinphos/parathion.

The WHO/IARC graphic below shows how the 2A (malathion, diazinon, and glyphosate) and 2B (tetrachlorvinphos and parathion) group classifications were derived based on the animal and human epi results reviewed by the IARC Panel.



David

-----Original Message-----

From: Miller, David

Sent: Friday, March 20, 2015 1:57 PM

To: Christensen, Carol; Britton, Wade; Rowland, Jess

Cc: Vogel, Dana

Subject: RE: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

Thanks, Carol.

I've attached the downloaded PDF of the article to make it simpler for folks.

David.

-----Original Message-----

From: Christensen, Carol

Sent: Friday, March 20, 2015 1:24 PM

To: Britton, Wade; Miller, David; Rowland, Jess

Subject: RE: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

FYI: http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(15)70134-8.pdf

---

From: Christensen, Carol

Sent: Friday, March 20, 2015 11:53 AM

To: Britton, Wade; Miller, David; Rowland, Jess

Subject: Lancet Oncology IARC summary (malation/diazinon/glyphosate/tetrachlorpvinphos)

Hi All

I just learned that the summary of the IARC-pesticide meeting is expected to be available on line around 1 pm today. FYI.

I think this is the link: http://www.thelancet.com/journals/lanonc/issue/current.

Carol

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

[TXR# 0008898]

OCT 30 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: SECOND Peer Review of Glyphosate

CAS No. 1071-83-6
EPA Chem. Code 417300
40 CFR 180.364
TOX Chem. No.: 661A
Reg Group: List A (6B)

FROM: William Dykstra, Ph.D. William Dykstra
Toxicology Branch I (IRS)
Health Effects Division (H7509C)

and

George Z. Ghali, Ph.D. G. Ghali 8/22/91
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Lois Rossi, Chief
Reregistration Branch
Special Review and Reregistration Division (H7508W)

The Health Effects Division Carcinogenicity Peer Review Committee convened on June 26, 1991 to discuss and evaluate the weight of the evidence on Glyphosate with particular emphasis on its carcinogenic potential. The Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based upon lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

1

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A. Individual in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated.)

Penny Fenner-Crisp	Penelope G. Fenner-Crisp
William L. Burnam	
Karl Baetcke	
Marcia Van Gemert	
Esther Rinde	
Hugh Pettigrew	
Marion Copley	
Lucas Brennecke	
George Ghali	

2. Peer Review Members in Absentia (Committee members who were unable to attend the discussion; signature indicates concurrence with the overall conclusions of the Committee.)

Reto Engler	
Richard Hill	—
John Quest	
Kerry Dearfield	
Yin-Tak Woo	
Jean Parker	— NONCONCUR
William Sette	
Robert Beliles	DO NOT CONCUR
Julie Du	

3. Scientific Reviewers (Committee or noncommittee members responsible for data presentation; signature indicates technical accuracy of panel report.)

William Dykstra	
Roger Gardner	9-5-91

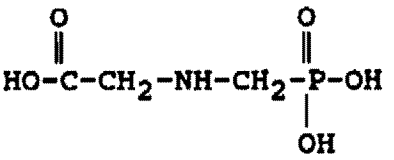
B. Background Information

Glyphosate is the isopropylamine (IPA) or sodium salt of N-(phosphonomethyl) glycine, marketed under the trade names of Roundup, Rodeo, Shackle, and Polado. Glyphosate is a wide spectrum plant growth regulator herbicide which is used to control grasses, sedges, and broadleaf weeds. It acts by the inhibition of amino acid synthesis.

Tolerances established for glyphosate and its aminomethyl phosphonic acid (AMPA) metabolite in 40 CFR 180.364 include the following:

IPA salt of glyphosate: soybeans, cotton, corn, sorghum, wheat, rice, vegetables, citrus fruits, pome fruits, stone fruits, tropical fruits, pastures, and alfalfa.

Sodium salt of glyphosate: sugarcane.



Glyphosate

On February 11, 1985, the carcinogenic potential of glyphosate was first considered by a panel (then called the Toxicology Branch Ad Hoc Committee) comprised of members of the Toxicology Branch of the Hazard Evaluation Division. The Committee, in a consensus review dated March 4, 1985, classified glyphosate as a Group C carcinogen based on an increased incidence of renal tubular adenomas in male mice. According to the consensus review, the tumor is rare, it occurred in a dose-related manner, and the incidence was outside the reported historical control range. The Committee also concluded that dose levels tested in a 26-month rat feeding study were not adequate for the assessment of glyphosate's carcinogenic potential in this species.

The kidney slides from the long-term mouse feeding study were subsequently reexamined, and one pathologist diagnosed an additional kidney tumor in control males. These findings were presented to the FIFRA Scientific Advisory Panel (SAP) which proposed that glyphosate be classified into Group D (inadequate animal evidence of carcinogenic potential). The SAP, in their meeting of February 11-12, 1986 (report dated February 24, 1986), concluded that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of

these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

HED deferred a decision on the repeat of an additional mouse oncogenicity study until the 1990 rat feeding study had been evaluated by the Peer Review Committee.

C. Material Evaluated

The material available for review consisted of a document prepared by Dr. William Dykstra summarizing major scientific and regulatory issues and relevant toxicology information, data evaluation records of a combined chronic toxicity/carcinogenicity study in rats and a carcinogenicity study in mice, the FIFRA Scientific Advisory Panel report dated Feb 24, 1986, a review of historical control data on mouse kidney tumors, a toxicology one-liner for the glyphosate data base and an OPP peer review report entitled "Consensus Review of Glyphosate" dated March 4, 1985.

D. Evaluation of Carcinogenicity Data

1. **Lankas, G. P. December 23, 1981. A Lifetime Study of Glyphosate in Rats. Unpublished report No. 77-2062 prepared by BioDynamics, Inc. EPA Acc. Nos. 247617 - 247621. MRID 00093879.**

a. Experimental Design

The lifetime feeding study in Sprague-Dawley rats at 50/sex/dose was conducted at dietary concentrations of glyphosate of 0, 30, 100, and 300 ppm. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in female rats were maintained.

b. Discussion of Tumor Data

An increase in the incidence of interstitial cell tumors of the testes was observed in male rats. Because of the absence of a dose-response relationship, the lack of preneoplastic changes, the wide variability in the spontaneous incidence of this tumor, the similarity in incidences between the high-dose

group and the historical controls, and lack of any evidence of genotoxicity, it was concluded by the previous Peer Review Committee that the observed incidence did not reflect a carcinogenic response.

Additionally, there was the question of possible thyroid carcinomas in high-dose females. After a review of the slides by a consulting pathologist, and a reassessment of all relevant data, including the fact that no effect of treatment on tumor latency or the combined incidences of adenoma and carcinoma was apparent, the earlier Peer Review Committee concluded that the data did not demonstrate a carcinogenic response in the thyroid.

c. Nonneoplastic Lesions and Adequacy of Dosing Considerations

No effect of treatment on the incidence of nonneoplastic lesions was noted. No effects of treatment on survival, body weight gain, clinical pathology, or findings at necropsy were noted. Therefore, there is no evidence that the highest dose tested was adequate to evaluate the carcinogenic potential of glyphosate.

2. **Stout, L. D. and Ruecker, F. A. (1990). Chronic Study of glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; Sept. 26, 1990. MRID No. 416438-01; Historical Controls; MRID No. 417287-00.**

a. Experimental Design

This chronic toxicity/carcinogenicity study in the rat was submitted to the Agency as a replacement study for the 26-month 1981 chronic toxicity/carcinogenicity study in the rat. In this study, randomized groups of 60 male and 60 female young (8 weeks old) Sprague-Dawley rats were fed dietary levels of 0, 2000, 8000, or 20,000 ppm or the equivalent of 0, 100, 400, and 1000 mg/kg/day of technical glyphosate for 2 years. At 12 months, 10 animals/sex/group were sacrificed.

b. Discussion of Tumor Data

Age-adjusted, statistical analyses of the tumor data are presented. The most frequently observed tumors in this study were pancreatic islet cell adenomas in males, thyroid C-cell adenomas and/or carcinomas in males and females, and hepatocellular adenomas and carcinomas in males. The following is a discussion of each type of tumor.

i. Pancreas (Tables 1 - 3)

Low-dose and high-dose males had a statistically significant increased incidence of pancreatic islet cell adenomas.

Table 1: Glyphosate - Sprague-Dawley Male Rats, Pancreatic Islet Cell Tumor Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	1/43[a]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
p =	0.159	0.409(n)	0.467(n)	0.472(n)
Adenomas	1/43	8/45	5/49	7/48[b]
(%)	(2)	(18)	(10)	(15)
p =	0.170	0.018*	0.135	0.042*
Adenomas/carcinomas	2/43	8/45	5/49	7/48
(%)	(5)	(18)	(10)	(15)
p =	0.241	0.052	0.275	0.108
Hyperplasia only	2/43	0/45	3/49	2/48[c]
(%)	(5)	(0)	(6)	(4)
p =	0.323	0.236	0.526	0.649

* Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

[a] First carcinoma observed at week 105, dose 0 ppm.

[b] First adenoma observed at week 81, dose 20000 ppm.

[c] First hyperplasia observed at week 91, dose 20000 ppm.

[d] $p \leq 0.05$; Fisher's Exact test with Bonferoni correction.

Note:
Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

6

Historical control data on the incidence of pancreatic islet cell adenomas from Monsanto's EHL are shown in Table 2 below.

Table 2: EHL 87122 - Historical Control Information for Histopathological Findings (All Deaths)

Terminal Necropsy Study	Months of Date	Study Length (Months)	No. Observed	No. Affected	% Affected
1	07/83	24	68	2	2.9
2	02/85	23	59	5	8.5
3	10/85	24	69	4	5.8
4	06/85	24	57	1	1.8
5	09/88	24	60	5	8.3
6	01/89	24	60	3	5.0
7	03/89	24	59	3	5.1

Committee's interpretation: Although the incidences of the pancreatic islet cell adenomas at the low-, mid- and high-dose groups exceeded the historical control range of 1.8 to 8.5 percent in male rats, there was no statistically significant positive dose-related trend in the occurrence of these tumors in males, no progression to carcinoma, and the incidence of hyperplasia was not dose-related. Therefore, the pancreatic islet cell tumors were not considered to be compound-related. It was also noted that the incidence of this lesion in the concurrent control for males was at the low end of the historical control range. The Committee concluded that the apparent statistical significance of the pairwise comparisons of the treated male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response.

The incidences of islet cell pancreatic tumors in the earlier rat study (Bio/dynamics Project No. 77-2062) are shown in Table 3. The incidence of pancreatic islet cell tumors for the two studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

Table 3: Incidence of Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Given Diets Containing Glyphosate for 26 Months (first rat feeding study).

Tumors	Dose (mg/kg/day) 0	3	10	30
Hyperplasia (%)	3/50 (6)	2/49 (4)	1/50 (2)	0/50 (0)
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Adenoma/carcinoma (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

ii. Thyroid (Tables 4 - 6)

C-cell adenomas were slightly increased in male and female mid- and high-dose groups as shown in Tables 4 and 5. Historical control ranges for the thyroid tumors in Sprague-Dawley rats were reported as shown in Table 6.

Committee's interpretation: Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

Table 4: Glyphosate - Sprague-Dawley Male Rats, Thyroid C-Cell Tumor Rates[+] and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	0/54	2/55[a]	0/58	1/58
(%)	(0)	(4)	(0)	(2)
p =	0.452	0.252	1.000	0.518
Adenomas	2/54[b]	4/55	8/58	7/58
(%)	(4)	(7)	(14)	(12)
p =	0.069	0.348	0.060	0.099
Adenoma/carcinoma	2/54	6/55	8/58	8/58
(%)	(4)	(11)	(14)	(14)
p =	0.077	0.141	0.060	0.060
Hyperplasia only	4/54	1/55	5/58[c]	4/58
(%)	(7)	(2)	(9)	(7)
p =	0.312	0.176	0.546	0.601

---

[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 54 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

[+] Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Table 5: Glyphosate - Sprague-Dawley Female Rats, Thyroid C-Cell Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Tests Results (p values).

Tumors	Dose (ppm) 0	2000	8000	20,000
Carcinomas	0/57	0/60	1/59[a]	0/55
(%)	(0)	(0)	(2)	(0)
p =	0.445	1.000	0.509	1.000
Adenomas	2/57	2/60	6/59[b]	6/55
(%)	(4)	(3)	(10)	(11)
p =	0.031*	0.671(n)	0.147	0.124
Adenoma/carcinoma	2/57	2/60	7/59	6/55
(%)	(4)	(3)	(12)	(11)
p =	0.033*	0.671(n)	0.090	0.124
Hyperplasia only	10/57[c]	5/60	7/59	4/55
(%)	(18)	(8)	(12)	(7)
p =	0.113	0.112	0.274	0.086(n)

---

[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 72 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

[+] Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

(n) Negative change from control.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If * then $p < 0.05$.

Table 6: Historical Control Data for the Incidence of Thyroid C-Cell Tumors in Sprague-Dawley Strain Rats.

Tumor	Range (%) Males	Females
Carcinomas	0.0 - 5.2	0.0 - 2.9
Adenomas	1.8 - 10.6	3.3 - 10.0
Hyperplasia	4.3 - 20.0	4.3 - 16.9

iii. Liver (Table 7)

There was a slight dose-related increase in hepatocellular adenomas in males but the incidence was within the range of historical controls from Monsanto's EHL. The reported historical control incidence of hepatocellular carcinomas ranged from 0 to 6.7%, and that for hepatocellular adenomas ranged from 1.4 to 18.3%. There were no dose-related increases in the incidences of other hepatocellular lesions.

Table 7: Glyphosate - Sprague-Dawley Male Rats, Hepatocellular Tumor Rates* and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	3/44	2/45	1/49	2/48[a]
(%)	(7)	(4)	(2)	(4)
p =	0.324	0.489(n)	0.269(n)	0.458(n)
Adenomas	2/44	2/45	3/49	7/48[b]
(%)	(5)	(4)	(6)	(15)
p =	0.016	0.683(n)	0.551	0.101
Adenoma/carcinoma	5/44	4/45	4/49	9/48
(%)	(11)	(9)	(8)	(19)
p =	0.073	0.486(n)	0.431(n)	0.245
Hyperplasia only	0/44	0/45	1/49[c]	0/48
(%)	(0)	(0)	(2)	(0)
p =	0.462	1.000	0.527	1.000

[a] First carcinoma observed at week 85 at 20,000 ppm.

[b] First adenoma observed at week 88 at 20,000 ppm.

[c] First hyperplasia observed at week 89 at 8000 ppm.

* Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Committee's interpretation: Despite the slight dose-related increase in hepatocellular adenomas in males, this increase was not significant in the pair-wise comparison with controls and was within the historical control range. Furthermore, there was no progression from adenoma to carcinoma and incidences of hyperplasia were not compound-related. Therefore, the slightly increased occurrence of hepatocellular adenomas in males is not considered compound-related.

c. Nonneoplastic lesions

There were no compound-related nonneoplastic lesions.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The HDT was 20,000 ppm which is the limit dose for carcinogenicity testing in rats. However, it appears that animals could have tolerated higher doses.

3. **Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamics Inc., dated July 21, 1983. Report No. 77-2061. EPA Acc. Nos. 251007 - 251009, and 251014.**

a. Experimental Design

Groups of 50 male and 50 female CD-1 mice were administered glyphosate in the diet at concentrations of 1000, 5000, or 30,000 ppm for 18 months.

b. Discussion of Tumor Data

Glyphosate produced an equivocal carcinogenic response in males characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

The Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee, in their meeting of February 11, 1985, tentatively classified glyphosate as a "Class C" carcinogen (report dated March 4, 1985). The kidney slides were reexamined by a consulting pathologist, and data were submitted indicating that an additional kidney tumor had been found in control males (the incidence in the control group was originally reported as 0/49 before the reexamination of the slides).

The Agency then requested that additional kidney sections from the mouse study be prepared and examined. The resultant microslides were examined by a number of pathologists. These examinations revealed no additional tumors, but confirmed the presence of the tumors identified in the original study report. The tumor in the control kidney was not present in any of the additional sections.

Because of the equivocal nature of the findings, the Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee asked the expert assistance of the FIFRA Scientific Advisory Panel (SAP) in determining the proper Weight-of-the-Evidence classification of the study. After reviewing all the available evidence, the SAP, in their meeting of February 11-12, 1986, proposed that glyphosate be classified as "Class D," or having "inadequate animal evidence of oncogenicity." The principal reason for this assessment by SAP was their determination that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

Committee's interpretation: In their meeting of June 26, 1991, the Health Effects Carcinogenicity Peer Review Committee concluded that despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females.

c. Nonneoplastic lesions:

Other nonneoplastic changes noted in high-dose male mice included centrilobular hypertrophy and necrosis of hepatocytes, chronic interstitial nephritis, and proximal tubule epithelial cell basophilia and hypertrophy in the kidneys of females. The no-observable-effect level (NOEL) for nonneoplastic chronic effects was the mid-dose level, 5000 ppm.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Glyphosate was tested in this study at levels higher than the limit dose. Body weight gain in males of the high dose was 13, 17 and 27% less than the controls at 3, 12 and 24 months respectively. The decrease in body weight gains was statistically significant ($p < 0.01$). This effect was less obvious in females. The doses tested were considered adequate for the carcinogenic potential assessment of glyphosate.

E. Additional Toxicology Data on Glyphosate

1. Metabolism

When Sprague-Dawley rats were given a single oral dose of C-14 glyphosate, 30 to 36 percent of orally administered glyphosate was absorbed.

Data showed that less than 0.27 percent of the dose was expired as CO_2 within 24 hours. Glyphosate, per se, was the highest radiolabeled material found in the urine and feces. The minimum level of glyphosate extracted from urine and feces was 97.5 percent. Amino methyl phosphonic acid (AMPA) was found in the excreta of animals at levels of 0.2 to 0.3 percent and 0.2 to 0.4 percent in urine and feces, respectively. No detectable AMPA metabolite was found in intravenously dosed rats and high dose, orally dosed rats. There were no other metabolites of glyphosate found.

Based on analysis of radioactivity in urine and feces and using the "sigma-minus" plotting method, males and females had alpha half-lives of 2.11 and 7.52 hours and 5.00 to 6.44 hours, respectively. The beta half-lives of males and females in these groups ranged from 69.0 to 181 hours for males and 79.9 to 337 hours for females.

Less than 1 percent of the absorbed dose remains in tissues and organs, primarily bone. Repeated dosing with glyphosate

does not significantly change the metabolism, distribution, or excretion of glyphosate.

N-Nitrosoglyphosate (NNG)

The Agency has determined that carcinogenicity testing of nitroso contaminants will normally be required only in those cases in which the level of nitroso compounds exceeds 1.0 ppm [see "Pesticide Contaminated with N-nitroso Compounds, proposed policy 45 FR 42854 (June 25, 1980)"]. The levels of NNG in technical glyphosate have been examined by HED. The overall NNG content in individual samples of technical glypnosate analyzed at production plants is shown below:

Samples Analyzed		NNG Observed
No. Samples	Per cent	(ppb)
2035	92.6	< 1000
124	5.6	1000 - 1500
24	1.1	1500 - 2000
13	0.6	2000 - 3000
2	0.1	> 3000

The overall data show that 92.6 percent of the individual glyphosate samples analyzed contain less than 1.0 ppm (1000 ppb) of NNG. TB concluded that the NNG content of glyphosate technical is not toxicologically significant.

2. Mutagenicity

Glyphosate has been tested in several mutagenicity assays and found to be negative in each of the three categories recommended for evaluating genotoxic potential. The acceptable studies include the following: Salmonella assay, both with and without S-9, up to toxicity or 5000 ug/plate, in vivo cytogenetic assay in rat bone marrow up to 1000 mg/kg, mammalian gene HGPRT mutation assay in CHO cells in vitro both with and without S-9 up to toxic levels (10 mg/mL) and rec assay with B. subtilis up to 2000 ug/disk.

Unacceptable studies which were also negative included DNA repair in rat hepatocytes between 0.0000135 and 0.125 mg/ml, and a dominant lethal assay in mice up to 2000 mg/kg.

3. Developmental and Reproductive Toxicity

In rats, doses up to 3500 mg/kg/day showed no evidence of malformations. Evidence of developmental toxicity in the form of unossified sternebrae and decreased fetal body weight was noted in fetuses from the high dose (3500 mg/kg/day). This dose was also toxic to dams as evidenced by weight gain

deficits, altered physical appearance, and mortality during treatment. The developmental and maternal toxic NOEL for this study was 1000 mg/kg/day.

In rabbits, doses up to 350 mg/kg/day showed no evidence of malformations. The highest dose tested was toxic to does as evidenced by altered physical appearance and mortality. No treatment-related developmental effects were noted. The NOEL for maternal toxicity is 175 mg/kg/day and the NOEL for developmental toxicity is 350 mg/kg/day.

In a three-generation reproduction study in the rat, the only toxicologically significant finding was focal renal tubular dilation in the kidneys of male pups from the F_{3b} generation of high-dose dams (30 mg/kg/day). The NOEL for this effect was 10 mg/kg/day. No effects on fertility, reproductive, or other study parameters were noted.

4. Structure - Activity Relationships

Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and reported to be negative.

5. Acute, Subchronic and Chronic Feeding/ Oncogenicity Data

Glyphosate is not considered to be toxic to mammals (rat oral LD_{50} of 4320 mg/kg (both sexes), and a dermal LD_{50} greater than 7940 mg/kg in rabbits).

A 1-year chronic feeding study in dogs at 6/sex/dose was conducted using doses of 0, 20, 100, and 500 mg/kg/day, administered by capsule. The NOEL for the study was 500 mg/kg/day (HDT).

F. Weight of the Evidence Considerations

The Committee considered the following findings to be of significance regarding the weight-of-the-evidence determination of the carcinogenic potential of glyphosate.

1. Glyphosate was associated with increased incidences of pancreatic islet cell adenomas in male Sprague-Dawley rats at all treatment levels in comparison to the concurrent control group (Table 1). Although the low- (18%), mid- (10%) and high-dose group (15%) incidences exceeded the 1.8 to 8.5% range of historical controls from Monsanto's EHL data base, the pancreatic islet cell adenomas were not considered

compound-related for the following reasons: a) there was no statistically significant positive dose-related trend in the occurrence of these tumors or in the incidence of hyperplasia in males over the wide range of dosing (2000 to 20000 ppm), and b) there was no progression to carcinoma. Tertiary evidence from the open literature cited by the registrant showed a range of 0 to 17% for pancreatic islet cell adenomas in Sprague-Dawley male rats for unadjusted data. The incidence of pancreatic islet cell tumors for the two rat studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

No increased incidence of these tumors was observed in female rats in comparision to concurrent controls.

2. C-cell adenomas were slightly increased in male and female mid- and high-dose groups in the rat (Tables 4 and 5). Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

3. There was a slight dose-related increase in hepatocellular adenomas in male rats (Table 7), but the incidence was within the range of historical controls from Monsanto's EHL. This increase was not significant in the pair-wise comparison with controls and there was no progression from adenoma to carcinoma. The incidence of hyperplasia was not compound-related. There were no dose-related increases in the incidences of other hepatocellular lesions. Therefore, the increased incidence of hepatocellular adenomas in males was not considered compound-related.

4. Glyphosate produced an equivocal carcinogenic response in male mice characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

Despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not feel that this lesion was compound-related.

5. Glyphosate was tested up to the limit dose in the rat, and up to levels higher than the limit dose in mice.

6. There was no evidence of genotoxicity for glyphosate.

7. Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and was reported to be negative.

G. <u>Classification</u>:

Considering criteria contained in EPA Guidelines (FR 51:33992-34003, 1986] for classifying a carcinogen, the Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based on lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

END

To: Brunsman, Lori[Brunsman.Lori@epa.gov]; Kidwell, Jessica[kidwell.jessica@epa.gov]
From: Rowland, Jess
Sent: Wed 9/23/2015 4:22:29 PM
Subject: RE: Glyphosate

Hi LB

Ex. 5 - Deliberative Process

JR

Sent from my Windows Phone

From: Brunsman, Lori
Sent: 9/23/2015 12:17 PM
To: Rowland, Jess
Subject: RE: Glyphosate

Jess –

Ex. 5 - Deliberative Process

Lori

****

Lori Brunsman, Statistician and Project Officer
Science Information Management Branch
Health Effects Division
Office of Pesticide Programs

Office of Chemical Safety and Pollution Prevention

Environmental Protection Agency
One Potomac Yard S-10934

brunsman.lori@epa.gov
703-308-2902

"When you have more than you need, build a longer table, not a higher fence."

From: Rowland, Jess
Sent: Friday, September 18, 2015 11:53 AM
To: Brunsman, Lori
Subject: Glyphosate
Importance: High

LB

Don't know if u r working at home or compressed. IF either, can u please do this for me Monday

Ex. 5 - Deliberative Process

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Rowland, Jess[Rowland.Jess@epa.gov]
Cc: Kidwell, Jessica[kidwell.jessica@epa.gov]
From: Powell, Calvin
Sent: Wed 9/23/2015 12:30:58 PM
Subject: RE: NEEDS CPR
Glyphosate CARC Final 9.21.15_cpr.docx

Hi Jess,

The re-formatted document is attached.

Regards,

Cal

Cal Powell

SEE Program Enrollee

Science Information Management Branch (SIMB)

Health Effects Division (HED)

Office of Pesticide Programs (OPP)

OCSPP/EPA

Room S-10935

One Potomac Yard (South Building), 2777 Crystal Drive, Arlington, VA 22202

703-347-0255 (voice)

703-305-0871 (fax)

From: Rowland, Jess
Sent: Tuesday, September 22, 2015 1:48 PM
To: Powell, Calvin

Subject: NEEDS CPR
Importance: High

HI

Feel free to do what you need to fix the paginations, formats and other stuff

Need it by 2:00 pm today.!!!! Just Kidding

COB tomorrow will be fine

Thank you very much

JR

Jess Rowland,

Deputy Director
Health Effects Division
703-308-2719

To: Kidwell, Jessica[kidwell.jessica@epa.gov]
From: Powell, Calvin
Sent: Wed 9/23/2015 11:29:49 AM
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'
Glyphosate CARC Final 9.21.15.docx

Hi Jessica,

Ex. 5 - Deliberative Process

Cal

Cal Powell

SEE Program Enrollee

Science Information Management Branch (SIMB)

Health Effects Division (HED)

Office of Pesticide Programs (OPP)

OCSPP/EPA

Room S-10935

One Potomac Yard (South Building), 2777 Crystal Drive, Arlington, VA 22202

703-347-0255 (voice)

703-305-0871 (fax)

From: Kidwell, Jessica
Sent: Wednesday, September 23, 2015 7:08 AM
To: Rowland, Jess; Powell, Calvin
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

Ok. Thank you.

From: Rowland, Jess
Sent: Tuesday, September 22, 2015 9:21 PM
To: Kidwell, Jessica; Powell, Calvin
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

Ludmilla
I am off tomorrow and Thursday...that why I wanted CPR to send it

Sent from my Windows Phone

From: Kidwell, Jessica
Sent: 9/22/2015 4:34 PM
To: Rowland, Jess; Powell, Calvin
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

Jess: Go ahead and share the file with me again. I'm not having any issues with other shared files, only the carc.

From: Rowland, Jess
Sent: Tuesday, September 22, 2015 4:05 PM
To: Kidwell, Jessica; Powell, Calvin
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

CPR

Ex. 5 - Deliberative Process

Sent from my Windows Phone

From: Kidwell, Jessica
Sent: 9/22/2015 2:26 PM
To: Rowland, Jess
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

Hi Jess: Can you send me the file as a backup. Your link works but it's not letting me edit in word for some reason. I'll need to call ez tech. If I can't get it to work correctly, I'll make edits on the file and email it to you.

From: Rowland, Jess
Sent: Tuesday, September 22, 2015 1:43 PM
To: Akerman, Gregory; Dunbar, Anwar; Brunsman, Lori; Chen, Jonathan; Kent, Ray; Liccione, John; McCarroll, Nancy; May, Brenda; Middleton, Karlyn; Kidwell, Jessica; Schlosser, Christopher; Wood, Charles; Woo, Yintak
Cc: Rowland, Jess
Subject: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

Here's the document that Rowland, Jess shared with you.

Open Glyphosate CARC Final 9.21.15.docx

Followthis document to get updates in your newsfeed.

To: Kidwell, Jessica[kidwell.jessica@epa.gov]; Powell, Calvin[Powell.Calvin@epa.gov]
From: Rowland, Jess
Sent: Wed 9/23/2015 1:20:47 AM
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

Ludmilla
I am off tomorrow and Thursday...that why I wanted CPR to send it

Sent from my Windows Phone

From: Kidwell, Jessica
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Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

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Sent: Tuesday, September 22, 2015 4:05 PM
To: Kidwell, Jessica; Powell, Calvin
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

CPR

Ex. 5 - Deliberative Process

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Cc: Rowland, Jess
Subject: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

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Open Glyphosate CARC Final 9.21.15.docx

Followthis document to get updates in your newsfeed.

To: Kidwell, Jessica[kidwell.jessica@epa.gov]; Powell, Calvin[Powell.Calvin@epa.gov]
From: Rowland, Jess
Sent: Tue 9/22/2015 8:05:22 PM
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

CPR

Ex. 5 - Deliberative Process

Sent from my Windows Phone

From: Kidwell, Jessica
Sent: 9/22/2015 2:26 PM
To: Rowland, Jess
Subject: RE: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

Hi Jess: Can you send me the file as a backup. Your link works but it's not letting me edit in word for some reason. I'll need to call ez tech. If I can't get it to work correctly, I'll make edits on the file and email it to you.

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To: Akerman, Gregory; Dunbar, Anwar; Brunsman, Lori; Chen, Jonathan; Kent, Ray; Liccione, John; McCarroll, Nancy; May, Brenda; Middleton, Karlyn; Kidwell, Jessica; Schlosser, Christopher; Wood, Charles; Woo, Yintak
Cc: Rowland, Jess
Subject: Rowland, Jess has shared 'Glyphosate CARC Final 9.21.15'

Here's the document that Rowland, Jess shared with you.

Open Glyphosate CARC Final 9.21.15.docx

Followthis document to get updates in your newsfeed.